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EUMYDRIN IN THE TREATMENT OF HYPERTROPHIC PYLORIC STENOSIS

AN ANALYSIS OF 40 CONSECUTIVE CASES

BY

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In the last few years the author has treated forty consecutive cases of hypertrophic pyloric stenosis with eumydrin (atropine methyl nitrate), which was brought to the notice of paediatricians in this country by Svensgaard in 1935. The analysis of this series has brought out certain points, which, had the writer realized them in time, would have improved the results. These factors are here discussed.

Clinical material

In order to review the results it is necessary to describe the clinical material. Every baby included was an undoubted case of hypertrophic pyloric stenosis. Diagnosis was based on the following points: (*a*) a history of large projectile vomits, associated with constipation; (*b*) visible gastric peristalsis; (*c*) in every case a palpable pyloric tumour, which varied in consistency under the examiner's hand; sometimes repeated examinations were necessary to elucidate this; (*d*) in thirty-four cases in which x-ray examination was carried out, delay in emptying the stomach. The delay, as usual, varied much in degree. In the majority it was marked, but in some clinically typical cases it was slight.

There were forty patients, nine girls and thirty-one boys, all treated at the Queen's Hospital for Children including two cases shown at the Royal Society of Medicine (Mackay, 1936). In half the cases, according to the mothers' history, projectile vomiting began under twenty-six days old, and the average age at onset was twenty-seven days (youngest seven days, oldest sixty-eight days). The onset of symptoms was usually sudden. In some babies small vomits occurred before the onset of projectile vomiting (probably independently of any pyloric obstruction), but these vomits have been ignored in calculating the averages. Probably those authors who state that vomiting is not uncommon in the first week have not made this distinction. The average duration of projectile vomiting before treatment was started was fifteen days (extremes three days and forty-two days, with one exception, in which it was said to be seventy-one days). In half the cases the vomiting had lasted less than fourteen days. At the beginning of eumydrin treatment the average age was forty-three days (half were under thirty-seven days, the youngest was seventeen days, the oldest eighty-six days). It is interesting to compare the age of these babies with the ages of 403 cases of pyloric stenosis admitted to the Hospital for Sick Children,

Great Ormond Street, between 1924 and 1930 (Paterson, 1931). The average age on admission to Great Ormond Street was forty-six days, so that this series does not suggest that diagnosis in London is now made at a much earlier age than ten or fifteen years ago. Paterson found that private patients, too, were diagnosed about the same age as his hospital cases.

The average weight at the beginning of treatment was 7 lb. 5½ oz. Only fifteen babies (37·5 per cent.) were over birth weight at the start of treatment; of the rest, three were under 6 lb. in weight. By Holt's standard (1926) the whole series averaged about 2¼ lb. under normal weight for their age.

As it chanced, fourteen out of forty babies, or 35 per cent., probably a higher proportion than usual, were suffering from some complication or were extremely feeble on admission. These complications included haematemesis, abdominal distension, collapse of lung with infection of that organ, pyrexia, boils, collapse of the baby, with irregular, somewhat gasping, breathing (symptoms usually attributed to alkalosis), prematurity and cyanotic attacks, and convulsions. All these complications were present before treatment.

The type of home from which the babies came may be judged from the fact that the hospital is in a poor district in the East End of London, and a large proportion of the fathers are unskilled or semi-skilled manual workers with small and often irregular wages, a material factor when considering the treatment of patients in their own homes.

Treatment adopted and its variations

All but two patients were admitted to hospital. An x-ray examination was made, usually on the day after admission, and generally eumydrin was not started until this was complete. Until latterly there was no fixed procedure as regards saline administration or gastric lavage, some babies receiving much saline and daily gastric lavage, some receiving neither. Feeds were given three-hourly, generally six feeds in twenty-four hours. Eleven babies, or 27·5 per cent., were fed on breast milk for all or a portion of the time of treatment. Failing breast milk, sweetened condensed milk was generally used, in a dilution (1 in 5 by volume) to provide 20 calories to each fluid ounce of feed; the feed being changed to dried milk when the baby was well on the way to recovery. The baby was given in the first few days rather less than his theoretical needs, but the aim thereafter was quickly to increase to an amount on which he could gain. A daily record was kept in the wards of food and fluid intake, but unfortunately some of these records were not preserved. The eumydrin solution (1 in 10,000 in water) was made up once a week, on account of its instability, and was given by mouth, usually half an hour, sometimes twenty minutes, before each feed. The first dose was usually 0·5–1·0 c.c. (0·05–0·1 mgm. per dose), increasing by 0·5 c.c. at each feed till a dose of 2·0–3·0 c.c., six times daily, was reached, i.e. 1·2–1·8 mgm. in twenty-four hours. Further increases were made if the vomiting was not checked. Only one baby was given eumydrin by lingual application of drops of 0·6 per cent. eumydrin in alcohol, as described by Wallgren (1940); this baby had one drop twice daily, or about 0·2 mgm. of eumydrin in twenty-four hours.

Results

(a) MORTALITY. Of the forty cases, five died during treatment; a sixth died of enteritis and pneumonia developed at home, i.e. four and a half weeks

after vomiting had completely ceased, and over seven weeks after the beginning of treatment. If this case is reckoned as cured of pyloric stenosis, then, on the basis of five deaths, the mortality was 12·5 per cent.; thirty-one cases, or 77·5 per cent., were cured by eumydrin, and four, or 10·0 per cent. more, were cured by operation after eumydrin had been tried for four to thirteen days. Of the five cases that died, four apparently responded to eumydrin, but developed an intercurrent condition; the fifth showed little response, was operated on on the thirteenth day, and, after operation, developed an enteritis of which he died. These cases are dealt with in greater detail later.

(b) VOMITING. Among the forty cases treated, the vomiting was stopped or markedly diminished by eumydrin in thirty-five or 87·5 per cent., though not all survived. These thirty-five showed a marked reduction in vomiting in an average period of 2·9 days; seven immediately, thirteen more within twenty-four hours, five more within two days, so that half the cases treated (twenty in all) had their vomiting much diminished in one day, and nearly two-thirds within two days. The longest period was seventeen days in a baby (J. van G., see page 4) acutely ill with a collapsed lung, and in this case much of the vomiting was presumably due to cough.

It is difficult to state the number of days within which vomiting due to pyloric stenosis completely ceased, for, when a careful record of all vomiting is asked for, the regurgitation of a drachm or two which would usually pass without comment is likely to be recorded as a vomit. In the thirty-one babies cured by eumydrin all vomits, big or small, were said to have ceased in an average period of twenty-five days. Of more value is the observation that, excepting for ' very small vomits,' or perhaps one or two large vomits in seven days, vomiting was stopped in an average period of ten days. For Svensgaard's (1935) cases, the comparable figure appears to be twenty-one days. In ten cases of the present series vomiting practically ceased within three days.

(c) GAIN IN WEIGHT. The thirty-one cases cured by eumydrin gained in the first week an average of 6·8 oz., and for five weeks an average of 6·9 oz. weekly. Of the whole series of forty, twenty-three gained 5 oz. and upwards in the first week, seven gained under 5 oz., nine lost weight, and one premature baby (J. W., page 14) had its true weight masked by oedema following excessive cooling of the body. The gain in weight of the babies responding rapidly to eumydrin was very good, for example, in the first week fourteen babies gained between 8 and 17 oz., and for a five-week period from starting eumydrin twelve babies averaged a gain of between 8 and 12 oz. weekly. It is interesting to compare these results with Svensgaard's. Her cases showed a loss of weight in the first week, and gained an average of 4·3 oz. weekly during an average stay of eleven weeks in hospital.

In considering the progress of a child great importance was given to the weight and general condition as well as to the vomiting, for a baby might improve considerably although continuing to vomit much. For example, two babies gained $5\frac{3}{4}$ and $5\frac{1}{2}$ oz. in the first week, though there was little obvious reduction in vomiting for six and ten days respectively, and both gained an average of over $6\frac{3}{4}$ oz. weekly for the five weeks after starting eumydrin. Excessive saline administration sometimes rendered the weights erratic and obscured one valuable check on progress.

(d) COMPLICATIONS OTHER THAN TOXIC EFFECTS. Complications already existing before treatment was begun have been mentioned. After admission seven babies developed diarrhoea in hospital (including one terminal diarrhoea), and of these four died (page 13). Four developed bronchitis, one otitis media (G. N., page 4), one a nasal discharge, and one (admitted with a collapsed lung) pneumonic changes in the collapsed lung immediately after admission (J. van G., page 4). All these made good recoveries. Two

babies (P. G., page 5, and B. L., page 5) had minor skin infections (boils and a papular eruption) on admission, and one (J. W., page 14) developed a small abscess in hospital. Two (G. N., page 4, and E. W., page 4) had haematemesis before eumydrin was given; two more (A. H., page 9, and E. C., page 14) developed it in hospital; one of the latter died (E. C., page 14). Two developed oedema, one (J. W., page 14) as a result of chilling, and the other (E. C., page 14) presumably from excessive fluid administration.

Progress of babies with a complicating condition on admission

Of the fourteen babies suffering from some complication before eumydrin was started, nine were cured by eumydrin, one by operation, and four died.

J. van G., male, aged twenty-four days, weight 6 lb. 15 oz., was admitted with the right lung collapsed, probably from aspirated vomitus. This baby was very ill in the early stages of treatment with infection of the lung, pyrexia, rapid breathing and cyanosis, and almost certainly would not have survived operation. His maximum dose of eumydrin solution was 5 c.c. six times daily (3·0 mgm. in twenty-four hours) and his food was chiefly sweetened condensed milk (1 in 5 by volume) His fluid intake was fairly liberal. Vomiting nearly ceased in thirty-two days, but not entirely for 106 days (fifteen weeks), and it was probably precipitated by cough for most of that time. In the ninth week of treatment the stomach was washed out and there was no residue. He was in hospital for eighty days on account of his lung condition, and ultimately made a good recovery. He gained an average of 5·6 oz. weekly for the first five weeks of treatment.

D. H., male, aged thirty-nine days, weight 7 lb., was admitted collapsed, wasted and approximately 3 lb. below birth weight. He had irregular and somewhat gasping respiration during the first twenty-four hours, i.e. symptoms presumably due to alkalosis. His maximum dose of eumydrin was 5 c.c. before each feed, and his food was sweetened condensed milk (1 in 5), with little fluid over and above that given in his feeds, except on the first day, when he had 10 c.c. of saline given subcutaneously. He improved fairly rapidly under eumydrin treatment. It is unlikely that surgical treatment could have saved his life. His average gain for five weeks was 5·5 oz. weekly, and the gain would have been larger had he not been underfed after discharge from the ward on the seventeenth day of treatment.

G. N., male, aged seventy days, weight 7 lb. 2½ oz., had had an unsuccessful Rammstedt operation at forty-six days old, which had failed to relieve the pyloric obstruction. He was having daily salines and gastric lavage and was steadily losing weight (about 1½ lb. since operation). He was suffering from pyrexia, haematemesis and poor appetite when started on eumydrin. His maximum dose of eumydrin was 2·5 c.c. six times daily, and his food was breast milk. He was given daily gastric lavage, and subcutaneous salines for the first twelve and nine days of drug treatment respectively. Vomiting was markedly reduced within twenty-four hours and he gained an average of 9 oz. weekly for the five weeks after starting eumydrin, in spite of developing otitis media.

K. S., A. T. and **E. M.** all had some abdominal distension or fulness before starting eumydrin; the first two did well, the third died (E. M., page 13).

E. W., female, aged thirty days, weight 7 lb. ¾ oz., had haematemesis on admission. Subcutaneous saline (about 5 oz.), was given daily for the first six days, and vomiting was not markedly reduced for six days, i.e. until the time when the fluid intake fell. Her maximum dose of eumydrin was 3·5 c.c. six

times daily, and her food was sweetened condensed milk. She gained an average of 8¼ oz. weekly for the first five weeks on eumydrin.

E. F., J. D. and **E. C.** had some pyrexia, without obvious cause, before the start of treatment. The last two died (J. D., page 13, and E. C., page 14).

J. W., a premature baby with a cyanotic attack with cessation of breathing before admission, died (page 14).

B. M., male, aged twenty-nine days, weight 6 lb. 6 oz., was wasted, feeble and sucked badly. He was given excessive subcutaneous saline (5 to 11 oz. daily), and his maximum dose of eumydrin was 5 c.c. six times daily. His vomiting was not much reduced until ten days after the start of eumydrin, and did not cease entirely until two months after the start of treatment. His haemoglobin was 46 per cent. (Haldane standard). In the fifth week of treatment he was given gastric lavage; the stomach was then emptying normally, and the lavage did not diminish the vomiting, but his appetite improved, perhaps as a result of the lavage, with a concurrent improvement in rate of gain in weight.

P. G. was suffering from boils. Eumydrin failed to cure him, and he was cured by operation (see page 8).

B. L. had a papular rash and blepharitis. She gained an average of 5½ oz. weekly on eumydrin.

Factors influencing the results of treatment

It is notorious that in cases of pyloric stenosis treated in hospital, the biggest cause of mortality is often infection acquired in hospital. To this the present series is no exception. Of the five babies who died, four had diarrhoea. But setting aside this subject, let us consider what factors can be shown to influence the response to eumydrin in the individual baby, as this should be of material help in deciding the line of treatment for each patient.

(a) Sex. With the small numbers available in this series it is not possible to say whether or not with eumydrin treatment there is any difference in prognosis for the two sexes. All five cases which showed no response to eumydrin were boys, but as boys made up nearly 80 per cent. of the total number no significance can be attached to this fact, especially since, if rate of gain in weight is considered, it is found boys gained slightly more rapidly than girls—the average gain in the first week was 7·2 oz. for the boys and 5·8 oz. for the girls. So far as this goes, it bears out Svensgaard's (1935) view that sex plays no part in the prognosis.

(b) Age and severity of onset, and age of treatment. Langstein in 1921 stated that if the symptoms of pyloric stenosis were fully established in the third week of life the prognosis for medical treatment was bad. On the other hand, Faxén (1933), after analysing 126 consecutive cases, all medically treated, failed to confirm this; he said that onset under twenty-one days old was not in his series associated with a longer total period of illness, nor, on the other hand, did early medical treatment appear to shorten the illness. These views were expressed before the days of eumydrin treatment. With eumydrin, Dobbs (1939) has emphasized that babies coming under treatment when very young respond less readily, thus supporting Langstein's view. This seems to be borne out in the present series, though, provided other conditions are favourable,

young babies may respond well. The two youngest babies both failed to respond and both were operated on (E. J., page 9, and B. D., page 9), the one was seventeen days old with three days history of vomiting, the other eighteen days with seven days history. Unfortunately both these babies had a high fluid intake which, as is shown below, was probably a contributory factor. The next in age was a twenty-two-day-old girl with a relatively small fluid intake, who did well. This certainly suggests that, with a much smaller fluid intake, the eumydrin might have had more effect in the first two. Of the five cases operated on because they failed to respond, four (P. G., B. D., A. H. and E. J., pages 8 and 9) were young babies, five weeks old or less, with the age of onset between eleven and twenty-two days old (the average age of onset for the whole series being twenty-seven days). On the other hand, the fifth case operated on after failure to respond to eumydrin (J. D., pages 9 and 13) was the oldest in the series, eighty-six days old at the beginning of treatment. In passing it is of interest that the youngest in the series, E. J. (page 9), who began to vomit at eleven days old, had two siblings, both of whom had been operated on for pyloric stenosis; a family history is considered by Langstein (1921) also of bad prognostic significance.

It is difficult to say whether or not rapidity and severity of onset influenced the results of drug treatment in this series. One is largely dependent on the mother's description for estimating the acuteness of onset, and both because of the uncertainties of history and on account of the other factors influencing progress, no final conclusion is possible. It is said that acute cases tend to come under treatment at an earlier stage in the disease because they are more readily diagnosed than more chronic cases. In this series there were twenty cases with a history of twelve days or less, and of these three failed to respond to eumydrin, and of the remaining seventeen all had the vomiting diminished by the drug, though four ultimately died. There were twenty cases with a history of fourteen to seventy-one days ; of these two failed to respond and eighteen were cured by eumydrin. So that these figures afford little evidence for or against the view that severity of spasm, as indicated by rapid onset of typical symptoms, makes the prognosis less favourable. Except perhaps in the youngest babies it seems unlikely, however, that the severity of spasm or vomiting was a major factor in determining the outcome. The following two cases show at least that an acute onset need not mean a less favourable response, or vice versa:

A. A., aged seven weeks, with eight days history of vomiting, had lost 1 lb. in weight in four days, and had ' vomited every feed for five days,' but gained at the rate of nearly 8 oz. weekly, the vomiting being checked by only 2·0 c.c. of eumydrin solution six times daily.

On the other hand, J. D. (page 13), aged twelve weeks, a relatively chronic case, with over a month's history of vomiting, and said to have had only three large vomits in seven days before admission, failed to respond to 2·5 c.c. of eumydrin solution and was operated on.

The degree of delay in emptying the stomach, as shown by x-ray examination before treatment, did not appear to bear any relation to the subsequent course of the case: this is in agreement with the views of other authors.

(c) FLUID INTAKE. Food was given in a concentration to provide 20 calories to 1 fluid oz., as in breast milk. The fluid intake and the food intake per pound body-weight have been calculated for each day of the first week of treatment, and once a week thereafter, for all those babies for whom the data were available. For the first week full data were available for twenty-eight babies. The average food intake per day per pound of body-weight varied between 1·8 oz. (for two babies with poor appetites) and 2·9 oz. (for two babies of low birth weight); the average total fluid intake per day per pound varied between 2·4 and 4·9 oz. In this analysis the babies have been grouped in two series, according to the amount of fluid intake in excess of the intake with food in the first week: (1) those getting 1·5 to 2·2 oz. of fluid per pound body-weight daily, over and above the amount given in the feeds, (2) those getting 1·3 oz. or less of fluid per pound body-weight besides that given in the feeds. Thus if a baby received daily per pound body-weight 2·5 oz. of breast milk and 3·0 oz. of fluid in all, his extra fluid was 0·5 oz. and he would go into the second group.

(1) In the first group, getting the large quantities of fluid (an average of 1·8 oz. per pound body-weight daily of extra fluid), there were twelve babies. Four babies (P. G., J. D., E. J. and A. H., pages 8 and 9) were operated on because eumydrin failed to relieve the obstruction; the other eight responded, in that their vomiting was markedly reduced in an average period of 5¼ days. There were four deaths in the group (J. D., E. M., E. C. and J. W., pages 13 and 14), and only five of these twelve cases were cured by eumydrin. Only two of the twelve are recorded as having good appetites, and seven had poor or very poor appetites. In the first week of treatment there was an average loss in weight of 1·9 oz.

(2) Contrast with this the second group of sixteen babies getting much less fluid (an average of 0·6 oz. per pound body-weight daily of extra fluid). Fifteen cases were cured by eumydrin and the sixteenth (M. L., page 13) was responding well until he developed enteritis. He was operated on and died, after eumydrin had relieved the pyloric obstruction. In every case the vomiting was markedly diminished by eumydrin, and in an average period of 1·7 days instead of 5¼ days. Twelve babies had good appetites and only two poor appetites. The average gain in the first week was 8·5 oz.

Of the remaining twelve babies in the series, for whom full details of fluid intake are not available, nine are known to have had little or no subcutaneous saline, two had liberal daily salines, and the quantity of saline given to the twelfth is not known. Adding these eleven to the cases described above in order to increase the numbers in the groups (see table), we have: (1) a group of fourteen babies with very liberal fluid intake, nine apparently responding to eumydrin and five unrelieved by it, with four deaths (three of them babies with enteritis); (2) a group of twenty-five babies with relatively small fluid intake, all responding to eumydrin, with an average gain of 8·1 oz. in the first week, marked reduction of vomiting in 1·3 days, and one death of which the primary cause was an infection.

These results, unless they simply reflect a larger administration of fluid to babies in the poorest general condition or making poor progress, indicate an adverse effect of high fluid intake. Certainly all babies getting high fluid did not start in poor condition. In some of them, large quantities of fluid, chiefly

INFLUENCE OF THE AMOUNT OF FLUID INTAKE ON THE RESPONSE TO EUMYDRIN

Fluid intake	HIGH	LOW OR MEDIUM
Number of cases	14	25
At start of treatment:		
Age in days	39	45
Weight	7 lb. 3½ oz.	7 lb. 7 oz
Number under birth weight	10	12
Responded to eumydrin: Number	9	25
Time in days in which vomiting was markedly reduced	4·8	1·3
Average gain or loss in first week	−1·0 oz.	+8·1 oz.
Cured by eumydrin: Number	6	24
No response to eumydrin : Number	5	0
Cured by operation: Number	4	0
Poor appetite: Number	8	2
Fatal cases: Number	4	1

as daily saline given subcutaneously, were pressed from the start, but on the other hand when infants continued to vomit and showed reluctance to finish their feeds the tendency was undoubtedly to continue subcutaneous salines, thus apparently continuing the vicious circle. The relative condition of the two groups at the start of treatment can in part be judged by a comparison of their average ages and weights. The average age of the group with smaller fluid intake was forty-five days and the average weight 7 lb. 7 oz.; the average age of the group with large fluid intake was thirty-nine days and the average weight 7 lb. 3½ oz.; i.e. the latter averaged six days younger and 3½ oz. lighter, which does not suggest their general condition was less satisfactory at the start of treatment. The same conclusion is borne out by a comparison of the notes on the clinical condition of the individual infants on admission. From a survey of the cases, the author feels in no doubt that a continued high fluid intake often produces poor appetite and also diminishes the effectiveness of the drug. The fact that all the five babies who failed to show any response to eumydrin received in extra fluid an average of 1·5 to 2·1 oz. per pound body-weight daily certainly suggests that a large fluid intake not only diminishes toxic effects but also diminishes the desired effect of the drug on the pylorus. The following are the cases that showed no response to eumydrin:

P. G., male, on admission aged thirty days, weight 7 lb. 14 oz. had boils on his legs. He was 12 oz. under birth weight. The stomach was washed out daily with normal saline, and he was given 10 to 20 oz. of subcutaneous saline daily. His weight owing to saline administration was increased by 10 oz. in two days before eumydrin was started. For the first week the food intake (sweetened condensed milk, 1 in 5) averaged, on account of poor appetite, only 2·0 oz. per pound daily, and his total fluid averaged 3·9 oz.: the extra fluid was therefore 1·9 oz. per pound body-weight daily. The maximum dose of eumydrin was 3·0 c.c. There was no reduction in vomiting. Weights were erratic on account of the large quantities of saline given parenterally. On the twelfth day instead of giving the drug by mouth 1 c.c. of eumydrin solution was given intramuscularly before feeds, but without relief of vomiting. On the thirteenth day a Rammstedt operation was carried out under local novocaine anaesthesia. During the operation the baby had a convulsion. The post-operative condition was poor with irregular breathing, but there was no laryngeal spasm and the Chvostek test was negative, so that there was no evidence

that the convulsion was due to tetany. It may have been due to novocaine (Bailey, 1940). From about the third day after operation progress was satisfactory.

J. D., male, aged eighty-six days, is dealt with on page 13. For the first week his average daily food intake was 2·4 oz. per pound body-weight, and his total fluid 4·5 oz., so that his extra fluid intake was high (2·1 oz. per pound). His appetite was poor. He was operated on after thirteen days on eumydrin on account of his failure to respond to the drug.

B. D., male, aged seventeen days, weight 6 lb. 8 oz., was in satisfactory general condition when put on eumydrin, and vomiting had started only three days before. Details of the food (breast milk) intake are not available, but he was given 5 to 15 oz. of saline subcutaneously each day during his six days on eumydrin treatment. The maximum dose of eumydrin was 5 c.c. There was no reduction in vomiting, he lost 9 oz. while on the drug, and he was operated on after one week. After the Rammstedt operation he still continued to vomit, though to a less degree. X-ray examination showed that there was now no delay in the emptying of the stomach. Vomiting temporarily improved when milk from another mother was substituted for that of his own mother, but did not cease until about seven weeks after operation.

A. H., male, aged thirty-five days, weight 7 lb. 8 oz., breast fed. For the first week his daily food intake averaged 1·9 oz. per pound body-weight, and his total fluid 3·6 oz., so that his extra fluid was 1·7 oz. per pound. He was given saline subcutaneously almost daily. There was no reduction in vomiting, and some haematemesis appeared. On the seventh and eighth days he was given gastric lavage without benefit. His maximum dose of eumydrin solution was 7 c.c. He was operated on with immediate relief of the vomiting.

E. J., male, aged eighteen days, weight 7 lb. 8 oz., was the third child in his family, and the first and second had also had pyloric stenosis and had been successfully treated by operation at the ages of three weeks and two months. There was no consanguinity of his parents. He had subcutaneous salines on the first day of treatment and thereafter rectal salines daily. His food intake (breast milk and sweetened condensed milk) averaged 2·4 oz. per pound body-weight, and his total fluid 3·9 oz., a difference of 1·5 oz. His appetite is recorded as ' very poor ' when his fluid intake rose to 4·6 oz. per pound body-weight. The maximum dose of eumydrin solution was 6 c.c. There was no reduction in vomiting, and he was successfully operated on on the sixth day. This baby was a fully established case of pyloric stenosis when first taken to hospital at the age of sixteen days, and in addition the disease was familial, factors which, as already stated, Langstein (1921) considers bad prognostic signs for medical treatment.

(d) GASTRIC LAVAGE. Svensgaard (1935) has abandoned gastric lavage, whereas Dobbs (1939) found it of great value. Of this series, eleven cases were started off with gastric lavage daily or almost daily, for a week and upwards, three more were given one to four wash-outs before or at the outset of treatment and the remaining twenty-four were started without gastric lavage. Which cases fell into each category was, generally, a matter of chance.

1. Of the eleven cases given regular gastric lavage from the start, two (P. G., page 8, and J. D., page 13) failed to respond to eumydrin and were operated on; the average gain for the rest for the first week was approximately 6 oz. (as compared with an average of 6·8 oz. for all the thirty-one cases cured by eumydrin), so that in rate of gain this group showed no superiority over the rest.

2. Of the twenty-seven not started with regular lavage three failed to respond

to eumydrin (B. D., A. H. and E. J., page 9), one of these (A. H.) was then treated with lavage, but without benefit, and all three were operated on. Four other babies in this group (J. van G., J. C., B. M. and G. B.), who were ultimately cured by eumydrin, continued to vomit for eight days and upwards and consequently were given gastric lavage. In two of these (J. van G., page 4 and J. C.) this continued vomiting was apparently independent of pyloric obstruction, and there was no gastric residue removed two-and-a-half hours after a feed, nor was there any benefit from the wash-outs; the third baby (B. M., page 5) showed an improved appetite and gain, possibly associated with the wash-outs, though the stomach emptied normally; in the fourth case (G. B), where there was still some delay in the emptying of the stomach one week after starting eumydrin, the institution of wash-outs coincided with a reduction in vomiting and a gain of 9½ oz. in the second week of eumydrin treatment. This was the only case in which there appeared to be immediate and sudden improvement from the gastric lavage, and a single case cannot prove its value.

Dosage of eumydrin

The maximum dose of eumydrin given to a baby has varied from 2 to 7 c.c. of 1 in 10,000 aqueous solution given before each of six, or occasionally seven, feeds in the twenty-four hours, or 1·2 to 4·2 mgm. of eumydrin in the day. In twelve babies cured by eumydrin 2·0 or 2·5 c.c. has not been exceeded, whilst two appeared to require 5 c.c. The five cases which failed to respond to eumydrin (see pages 8 and 9) received 2·5, 3·5, 5·5, 6 and 7 c.c. respectively as their maximum dosage, and one (P. G.) was given intra-muscular injections of 1 c.c. of the solution before feeds without obvious effect. Larger doses might have proved effective, at least in the first two cases, but so far as the writer's limited experience goes, increases in dosage over 4 c.c. have usually seemed of doubtful value. There were only two babies (E. J. and A. H.) who were given 6 and 7 c.c. and in both cases these large doses, like the smaller, failed. In the single case treated with lingual application of the alcoholic solution (0·6 per cent.), approximately 0·1 mgm. of eumydrin given twice daily was accompanied by immediate reduction in vomiting. This dose was only one-sixth of the smallest ' maintenance dose ' as given in aqueous solution.

Treatment given in cases which responded favourably

The babies who responded really well to eumydrin in aqueous solution had treatment more or less as follows:—

1. The daily food intake for the whole of the first week added together averaged between 2·1 and 2·7 oz. per pound body-weight daily (this food containing 20 calories per fluid ounce).

2. The extra fluid in the first week did not usually exceed an average of 1 oz. per pound body-weight daily (over and above that given in the feeds), and might be cut out entirely after the first few days. During the first one or two days some extra fluid certainly diminished toxic effects.

3. Some had gastric lavage, some not, with little obvious influence on the results.

4. The maximum dose of eumydrin solution varied between 2 and 5 c.c.

given before each feed: the drug was begun with 0·5 to 1·0 c.c. in order to minimize the risk of toxic effects.

Below are given the histories of a typical case with good response (K. S.) and a typical case with poor response (J. K.) to eumydrin:—

GOOD RESPONSE. K. S., male, aged thirty days, weight 6 lb. 9 oz., breast fed. The baby on admission was thin and had some abdominal distension. The stomach was washed out before eumydrin was begun, and he was given 11 oz. of subcutaneous saline during the first twenty-four hours in hospital, and none thereafter. For the first week he received daily per pound body-weight an average of 2·1 oz. of food and 2·4 oz. of fluid. The maximum dose of eumydrin was 3 c.c. Vomiting was markedly less from the time the first dose was given, there were in all only four vomits in the first five days and none thereafter. He was eleven days in hospital, but had forty-six days' treatment. He gained $6\frac{1}{4}$ oz. in the first week and an average of 8·1 oz. weekly for the first five weeks.

POOR RESPONSE. J. K., male, a twin, aged thirty-seven days, weight 6 lb. He was fed chiefly on breast milk. He did not begin to vomit until twenty-eight days old and was a typical case of hypertrophic pyloric stenosis. His condition was fairly good on admission. He had gastric lavage (with normal saline) daily for thirty-six days, and was given subcutaneous saline daily for thirty-one days. For the first week he received daily per pound body-weight an average of 2·2 oz. of food and 4·4 oz. of fluid in all. Appetite was poor and tube feeding was resorted to. Vomiting was markedly less in two days but was not stopped; it nearly ceased in thirty-four days. He was in hospital for forty-five days and had eighty-three days' eumydrin treatment. He gained $1\frac{3}{4}$ oz. in the first week and an average of only $2\frac{3}{4}$ oz. weekly for the first five weeks.

His twin sister, V. K., vomited from the first week of life, but her vomiting was not projectile, there was no visible peristalsis and when she died at thirty-seven days old autopsy showed her to have the first part of the duodenum much dilated, with a narrowing of the gut just beyond, so that at the junction of the first and second part of the duodenum the lumen just admitted a probe. The pylorus was normal. Dr. Alice King, under whom this baby was admitted, kindly allows the author to quote this case.

The first baby, K. S., had a relatively low fluid intake and no gastric lavage after the drug was started, his vomiting was rapidly checked, he had a good appetite and gained well. The second baby, J. K., had a grossly excessive fluid intake, and daily gastric lavage; vomiting, though much less, continued until after the salines were omitted. His gain in weight was slow. Incidentally, the family history of J. K. is interesting; both twins had a defect in the same region of the intestinal canal, in one case a stenosis of the duodenum with a normal pylorus, in the other a hypertrophic pyloric stenosis.

Toxic effects

Svensgaard's article in 1935 laid stress on the need of ' saline administration while the patient is still in a dehydrated condition,' with the object of avoiding the toxic effects of eumydrin, and paediatricians in this country have emphasized the same point. In Svensgaard's own series there were no serious toxic symptoms, but she mentioned one fatal case of eumydrin poisoning with hyperpyrexia, perhaps due to idiosyncrasy reported by Friedlaender. Monrad (1938) has had one death from eumydrin poisoning. The baby was having in all 3·5 mgm. of eumydrin daily and suddenly developed nystagmus, dilated

pupils, a high temperature, restlessness and convulsions. In a series of sixty-four cases treated with eumydrin Monrad has had nine cases of fairly severe toxaemia with high temperature in every case, and restlessness, nystagmus and convulsions recorded in two cases. The dose of eumydrin was 3·5 to 4·0 mgm. daily.

The toxic effects observed in the present series have been a rise of temperature, pulse and respiration rate, a bright red flush, slight dryness of the mouth, slight dilatation of pupils, abdominal distension and constipation. Fifteen babies in the series are noted as showing some toxic effect, which might be only a bright red flush lasting for an hour or more, or almost any combination of the above symptoms; e.g. one baby had a transient pyrexia of 105·4° F., without flush or other symptoms, another a flush and dry mouth without recorded pyrexia, another a flush, abdominal distension, dilated pupils, and rise of respiration and pulse rate, with the rectal temperature only 99·4° F. Usually the symptoms appeared in babies not having subcutaneous salines, and they were simply treated by omitting or halving the next dose of eumydrin. These transient symptoms in no way interfered with the baby's progress. It should be noted, however, that the initial dose of eumydrin was usually only 0·5 to 1·0 c.c. of the solution, i.e. 0·05 to 0·1 mgm.

There is one symptom, however, which may be of serious significance, and that is abdominal distension, a symptom also observed with atropine (Parsons, 1933), and all those using this drug should be aware of its possible dangers. Seven babies in this series are noted as having some abdominal fullness or distension, sometimes once only, sometimes on a number of occasions while on eumydrin, and probably transient fullness sometimes went unrecorded.

One baby (M. L., page 13) developed paralytic ileus. He was operated on during the course of enteritis, and paralytic ileus followed. Probably diarrhoea, perhaps on account of the resulting fluid imbalance, favours the development of this toxic effect, for the only other case of gross abdominal distension (E. M., page 13) was also in a baby with enteritis. This baby had some abdominal fullness necessitating reduction of the food intake, before eumydrin was given at all, and distension recurred and become severe with the onset of diarrhoea. In both cases the total dose of eumydrin was only 1·5 mgm. in twenty-four hours. In both cases severe distension could probably have been avoided had the drug been reduced when the toxic effect was first observed. The drug, moreover, in each case had markedly reduced the vomiting with a good gain in weight during the first week of treatment. Dobbs has also reported a case of paralytic ileus in a baby weighing 5½ lb. and given 7 c.c. of eumydrin before each feed, probably 4·2 mgm. in twenty-four hours. Although few reports of paralytic ileus following eumydrin treatment have been published the author has heard indirectly of some other cases in this country. In these, as in the author's case, the early and easily treated symptoms of abdominal distension were apparently ignored and the drug continued, perhaps in large doses, until the condition was irrecoverable. Abdominal distension is always an indication for immediate reduction, or temporary omission of eumydrin, and it would be a wise precaution when operation is undertaken after a course of eumydrin to omit the drug for twenty-

four hours before operation. Apart from the presence of toxic effects of the drug, which may be accentuated by diarrhoea, administration of eumydrin is not contra-indicated if a baby develops loose stools; in none of the cases in this series has eumydrin produced or worsened an existing diarrhoea; on the contrary, it sometimes produces constipation.

Lindberg (1925) has shown that if a given dose of atropine is continued the rate of elimination increases, so that a progressively larger dose is needed to produce toxic symptoms. The same probably holds true of eumydrin. Lindberg has said of atropine, and recently Wallgren (1940) of eumydrin, that toxic symptoms are more likely with an aqueous solution taken into the stomach, than by the lingual administration of an alcoholic solution. They state that, when an aqueous solution is given uncertainty of effect is produced by vomiting, varying dilution from gastric retention and varying potency of the solution from deterioration with keeping; and that the dose necessary for control of vomiting is much smaller when the alcoholic solution, absorbed through the tongue, is given.

Fatal cases

The following are the histories of the five babies who died:

J. D., male, aged eighty-six days, had some pyrexia on admission, was lethargic, wasted and weighed 7 lb. 9 oz. He had thirty-one days' history of vomiting, but was said to have had only three large vomits in the seven days before admission. He was fed on breast milk and sweetened condensed milk and his maximum dose of eumydrin was 2·5 c.c. He had large quantities of subcutaneous saline daily (an average total fluid intake of 4·5 oz. per pound body-weight daily for the first week), and daily gastric lavage. Though vomiting diminished, the obstruction at the pylorus persisted, as shown by the presence of 4 to 9 oz. of food in the stomach two-and-a-half hours after a meal, and consequently surgical treatment was adopted. His weight was erratic on account of the large amounts of saline given, but his general condition at the time of operation, thirteen days after the start of eumydrin, was better than on admission. On the third day after operation the stools were fluid, he rapidly became dehydrated and died next day of enteritis contracted in hospital. In this case eumydrin probably failed on account of the excessive fluid intake, but death was due to cross-infection after operation.

E. M., female, aged thirty-six days, weight 6 lb. 8 oz., had some abdominal distension on admission and was 12 oz. under birth weight. The food was sweetened condensed milk (1 in 5), and the total fluid intake for the first week averaged 4·4 oz. per pound body-weight daily. The maximum dose of eumydrin was 2·5 c.c. The vomiting was markedly less within twenty-four hours and she gained $6\frac{1}{4}$ oz. in the first week. About the end of that week she developed diarrhoea at a time when the writer had gone on holiday. By the middle of the second week there was marked abdominal distension with fluid stools and vomiting. Eumydrin was continued. A Rammstedt operation was done on the fourteenth day when the baby was very ill with gastro-enteritis and abdominal distension. She collapsed and died the same night. In this case, in spite of a high fluid intake, eumydrin would presumably have cured the baby had it not been for cross-infection. Diarrhoea apparently precipitated the distension caused by eumydrin. Death was due to gastro-enteritis and to operation, and was probably accelerated by the abdominal distension.

M. L., male, aged thirty-seven days, weight 7 lb. 13 oz., started treatment

when in fairly good general condition, and was fed on sweetened condensed milk. He appeared to be responding well to 2·5 c.c. of eumydrin with an average daily fluid intake of 2·9 oz. per pound body-weight, and gained 7¼ oz. in the first week. In the second week he developed acute enteritis, probably from E. M. (see above) who was in the ward at the same time, and by the fourteenth day he had lost 12 oz. in weight and the abdomen was distended. In the absence of the writer, the abdominal distension was not taken as an indication to reduce the eumydrin, and on the twenty-first day the baby was operated on. The stools were fluid, the abdomen grossly distended and the baby acutely ill. He died next day with paralytic ileus. Death here, too, was primarily due to enteritis in a baby previously responding to eumydrin. The ultimate cause of death was paralytic ileus. The paralysis of the gut must be attributed to a combination of factors: (a) enteritis, (b) continued administration of eumydrin after the appearance of distension, and (c) the inevitable handling of the grossly distended gut at operation.

E. C., male, aged sixty-one days, weight 8 lb. 1 oz., was breast fed, and, though thin, in satisfactory condition on admission. Nevertheless he was given saline subcutaneously daily, and for the first week the average daily fluid intake totalled 4·4 oz. per pound body-weight. He did well at first on 2·5 c.c. of eumydrin, but, probably on account of the excessive fluid intake, vomiting recurred on the eighth day, and there were some large vomits daily. Three weeks after treatment started there was a sudden deterioration in the general condition, ushered in by some small vomits containing blood. Next day the baby was collapsed and oedematous, with constant dribbling vomits, and he died the same day. The excessive fluid intake was probably the cause of death in this case. Post-mortem examination showed only oedema of the tissues and some free fluid in the abdomen in addition to wasting and the typical changes in the pylorus.

J. W., male, aged thirty-three days, weight 5 lb. 6 oz., was a premature baby. He had had a cyanotic attack with cessation of breathing in the maternity hospital before admission to the Queen's Hospital. His maximum dose of eumydrin was 3·0 c.c. and he, too, received excessive quantities of saline subcutaneously. He developed a small abscess in the buttock. Four days after starting treatment his temperature fell to 93° F. and he was found collapsed. Thereafter he did badly. Next day he was oedematous as a result of the chilling, and he died with diarrhoea about two weeks later.

Thus the primary cause of death in three out of the five cases was an infective diarrhoea acquired in the hospital, and in two cases a contributory cause was failure to reduce the eumydrin when abdominal distension was observed, leading in one case to paralytic ileus. In one case the cause of death was uncertain, but was probably excessive fluid administration. In the premature baby a subnormal temperature and oedema were followed by a terminal diarrhoea.

Duration of treatment

The average duration of eumydrin treatment for the cases who recovered was fifty-six days, eight weeks exactly. Probably this was unnecessarily long. The average duration of treatment in fifteen cases successfully treated by Braithwaite (1938) was five-and-a-half weeks (extremes two-and-a-half and twelve weeks). Still stated in 1923 that with cases medically treated gastric lavage was generally required for three to four months, which would make the

baby, say five months old at the end of the treatment, i.e. when spontaneous recovery occurred. Four cases in the present series were stopped in less than four weeks; three (A. H., B. W. and B. L.) stopped after seventeen, twenty-three and twenty-seven days respectively at the ages of eighty-two, ninety-three and seventy-nine days, and had no return of vomiting; the fourth (J. P.) stopped after twenty-four days when seventy-one days old, had two vomits in the next seven days and a sharp recurrence of symptoms in the week after, for which he was re-admitted and given a further course of treatment. After this case the tendency was to leave well alone, and keep the baby on the drug a good deal longer, only reducing it gradually. In about half the cases the drug was stopped under three months old, i.e. much younger than spontaneous cures can usually be expected. The apparent carry-over of eumydrin effect is interesting and is discussed later.

Time in hospital

All but two babies were treated as in-patients. The average time in hospital for the in-patients successfully treated with eumydrin was twenty-eight days; seven babies were in for seven to eleven days; fourteen for twenty-one days or less. Of the rest, two were kept in for several weeks after being ready for discharge because of illness in their homes; two were from hostels for unmarried mothers, and, on account of difficulties in supervision in the hostels were kept in hospital for fifty and sixty days respectively, and one baby admitted with collapse of lung followed by pneumonia (J. van G) was in for eighty days on account of his lung condition. These five cases, averaging fifty-four days each in hospital, would most probably have been in as long if treated surgically. If these are excluded, the average stay of the rest was twenty-three days. With more knowledge of the drug, this time could be much reduced.

The author early on gave directions to one mother in the out-patient department for her baby's treatment at home. Unfortunately, the mother had been told by another doctor before her visit to hospital that operation was essential, and she never attended again. Two other babies have been treated to a conclusion without admission. In one case directions were simply given in the out-patient department, the baby recovered, but treatment was irregular and progress slow. The other mother with her baby attended in a ward daily for the first five days for instruction, and her infant made excellent progress. It should be noted that in spite of the fact that the parents were for the most part in poor economic circumstances, the mothers of nearly all babies successfully coped with the treatment at home after the initial period in hospital.

Discussion

'The pylorus will open up spontaneously in time and the child recover, provided he does not die in the process. When recovery occurs in this way we know, from the results of post-mortem examination, that the muscular coat remains thickened for a long time after its action has become quite normal.'

. . . ' When once the gain in weight has begun, it is usually rapid and continuous and the child is soon practically well.' So wrote that careful observer, John Thomson, in 1925. If cessation of vomiting is fairly sudden, so also is the onset of projectile vomiting. Not infrequently the mother can say to an hour when projectile vomiting started. The hypertrophy of the muscle obviously cannot develop suddenly, yet within three days of the onset of vomiting, the typical pyloric tumour may be felt. The present writer has seen a baby with all the typical symptoms and signs of pyloric stenosis suddenly cease to vomit without treatment, and progress normally for between one and two weeks, only to have a sudden return of symptoms, which were then cured by the Rammstedt operation. Again if a baby with pyloric stenosis develops a severe gastro-enteritis the vomiting may cease to have the typical projectile character, visible gastric peristalsis may greatly lessen and the pylorus may no longer be palpable. These facts can only be explained by supposing that it is spasm of the hypertrophied muscle which determines the presence or absence of the typical symptoms, that this spasm can appear and disappear suddenly, and that some unknown factor spontaneously causes a disappearance of spasm, it may be fairly suddenly, say between three-and-a-half and five months old, in those babies that survive as long. Obviously eumydrin, like atropine, can remove this spasm. In this series eumydrin was probably continued unnecessarily long, yet in about half the cases the drug was stopped when the baby was between five weeks and three months old, and there was no recurrence of symptoms, and this is much younger than a spontaneous disappearance of symptoms can generally be expected. Lindberg (1925) using atropine in alcoholic solution states that a single course of only one to three weeks stopped the symptoms for good in some of his cases. Again, there seems a curious ' carry-over ' of the influence of eumydrin: toxic symptoms, such as flush and pyrexia, are transient, usually disappearing in a few hours, so one would expect the effect of the drug on the pylorus would last about a similar length of time, and it seems unlikely that a small dose of eumydrin, given once or twice in twenty-four hours, and producing no toxic effects, can exert an anti-spasmodic effect for the whole twenty-four hours. Yet Lindberg (1925) gave his alcoholic solution of atropine once to five times daily with satisfactory results, and Wallgren (1940) successfully treats his cases with one dose in twenty-four hours of 0·1 to 0·5 mgm. of eumydrin in alcohol applied to the tongue. Following his article, the writer has treated a single case with two doses in the day of 0·1 mgm. each, with extremely satisfactory results. Not only may the effect of one small dose last for a day but vomiting may be checked for many days after the drug is stopped. When J. P.'s medication was stopped after twenty-four days' treatment there were only two vomits in the first week, followed by a sudden relapse in the second week. Dobbs describes a case in which the drug was stopped after twenty days' treatment. There was no vomiting for eighteen days, and thereafter a return of vomiting. Rinvik (1940) has had cases showing recurrence apparently twenty to twenty-nine days after eumydrin was stopped. These facts taken together suggest that temporary allaying of the spasm may allow the disappearance of the factor causing it for a longer or shorter period.

Does a temporary anti-spasmodic effect break some vicious circle which produces the spasm? Perhaps the opening of the pyloric canal allows a return to normal of some chemical balance in the stomach.

Two facts seem to prove that eumydrin exerts its anti-spasmodic effect on the pylorus after absorption into the blood stream and not (as when instilled into the eye) by direct action at local nerve endings. These are: (1) that lingual application of a drop or two of the drug in alcoholic solution will check vomiting; (2) that excessive parenteral saline diminishes the effectiveness of eumydrin presumably by hastening elimination. Perhaps the action of eumydrin may help to elucidate the mechanism of normal physiological control of the passage of food through the pylorus (a subject on which, as Vertue (1939) has pointed out, views are still conflicting), as well as the pathogenesis of hypertrophic pyloric stenosis.

A high fluid intake appears to diminish all the effects of the drug. Not only this, but excessive fluid administration is likely to be accompanied by failure of appetite. Thus, though a fairly liberal fluid intake immediately before eumydrin is started will diminish the toxic effects, a continued high intake is contra-indicated, and was, probably, the cause of the failure of the drug to relieve spasm in five cases, and of its relatively slow action in others in this series.

The most dangerous toxic effect is probably abdominal distension. The two cases of acute abdominal distension in the series were suffering from enteritis at the time. The distension may have been caused by fluid imbalance resulting from the diarrhoea, but a large fluid intake did not prevent the distension. The distension was accompanied by continued pyrexia, possibly due to the drug, but there was no red flush, or dilated pupils, another instance of how the various toxic effects occur singly or in different combinations.

The number of cases here published, forty in all, is not large, and obviously the mortality rate in a series of this size may be misleading, so it is worth adding together the results of several workers in this country. Taking all the cases yet published in series of twenty-one and upwards [Braithwaite (1938), twenty-one cases; Dobbs (1941), forty cases; Vertue (1939), twenty-one cases; present series, forty cases], we get 122 cases with fourteen deaths, a mortality of 11·5 per cent.; ninety-three cases or 76·2 per cent. were cured by eumydrin, and fourteen or 11·5 per cent. by operation after a course of eumydrin treatment, and one or 0·8 per cent. by another drug. The great majority of the 122 cases were hospital patients. Lightwood (1939) and Findlay (1938) have published a further seventeen cases cured by eumydrin with no deaths.

Because of the risks of hospitalization in most countries, a distinction is usually drawn between the mortality rate of hospital cases and the mortality rate of private patients (Thomson, 1925; Herzfeld and Wallace, 1935). The unpalatable but well-known fact that the main mortality in most large series of cases in this country is often due to infection acquired in hospital was well brought out by Paterson in 1931. In the Hospital for Sick Children, Great Ormond Street, the year's mortality had never dropped below 21 per cent., and for the seven years 1924 to 1930 (403 cases in all), it remained roughly stationary

and averaged exactly one death in every four patients admitted. Of fifty private patients of the same average age operated on by the same surgeons and apparently supervised by the same physicians in nursing homes, however, not one died. But of twelve private patients of Paterson's admitted to hospital, again one in four died. Some children's hospitals in other countries have diminished their cross-infection rate far below ours, as witness the fact that Svensgaard reporting sixty-one cases kept an average of seventy-seven days each in hospital, lost only one baby from infection, a case of pyelo-nephritis, and is able to make a statement that astonishes a British paediatrician, namely that: ' the infant itself misses nothing by staying in the hospital.' A mortality rate of 20 to 25 per cent. is probably not unusual in children's hospitals in this country for surgically-treated cases (Parsons and Barling, 1933; Wallace and Wevill, 1934; Herzfeld and Wallace, 1935; Braithwaite, 1938), but a considerably lower rate can be claimed for some large series. In the last five years large series have been published by Thompson and Gaisford (1935), 209 cases; Jewesbury and Page (1937), 303 cases; and Tallerman (1938), 98 cases. The great majority were hospital patients, and among this total of 610 cases there were eighty-two deaths, a mortality of 13·4 per cent. If the mortality among large series of babies treated by the Rammstedt operation by trained hospital teams is, say, 13 to 25 per cent. in this country, we can be fairly sure that the total morbidity in the country averages considerably higher. With expert teams the direct operative mortality is known to be small, but a surgeon's opinion on the operative skill necessary is of interest. Lake has said: ' It is the type of operation in which only practice makes perfect . . . simple as it appears, there are many pitfalls for the inexperienced,' and few surgeons unconnected with a children's hospital can gain any large experience. Some of the immediate post-operative troubles occasionally met with are persistence of symptoms due to inadequate division of the muscle, haematemesis immediately following operation, particularly perhaps where there has been additional handling (for instance following accidental puncture of the mucous membrane) and cutting out of sutures in the abdominal wall, not to mention the risks inseparable from any major operation. Hence it is probable that in the country as a whole the direct operative mortality among babies treated by the Rammstedt operation is not small, and to this must be added the mortality from hospitalization.

The mortality of 11·5 per cent. for 122 cases, nearly all hospital or clinic patients, treated with eumydrin in this country compares favourably with anything heretofore achieved in large series of cases in Great Britain by operation. With the experience now being gained it should, however, be possible to reduce the mortality considerably, by treating cases without admission to hospital whenever possible, by avoiding excessive fluid administration and thereby improving the response to eumydrin and shortening the time in hospital, and by vigilance in avoiding dangerous toxic effects, such as excessive abdominal distension or hyperpyrexia.

In the Scandinavian countries it seems that eumydrin has already largely displaced other methods of treatment, and its use is spreading from there to

other countries (Türck, 1939; Landor, 1939). Svensgaard's mortality was 3·3 per cent. for sixty-one cases and Wallgren, using the drug in alcoholic solution, applied to the tongue, states that the total mortality rate of Gothenburg infants suffering from pyloric stenosis has been reduced to 1 per cent. for the past twelve years. So there is still much room for improvement in results in this country.

Simpler methods of treatment, if efficacious, are obviously preferable to more complicated ones, and eumydrin therapy is steadily growing in favour. Its wide adoption in this country should greatly diminish the total mortality from pyloric stenosis. Whether medical or surgical treatment is employed, success will always in large measure depend on the physician and his familiarity with the medical treatment involved.

In this series an aqueous solution of eumydrin has been used; it may be that an alcoholic solution in much smaller dosage for lingual application will prove the more effective method, as Wallgren (1940) holds. If drop doses are given by a mother with a pipette, there is, of course, the possible danger of double or quadruple the intended dose being given, though some practice with a pipette and plain water should render such errors unlikely. Nevertheless an aqueous solution in bigger volume will probably prove the method of choice at least when the mother's accuracy is doubted. In that case, the routine suggested is as follows: The baby, unless obviously dehydrated, should receive fluid by mouth only, perhaps 3 oz. per pound body-weight (inclusive of his feeds), in the first twenty-four hours, and thereafter only so much water, over and above that in his feeds, as he really wants to take. The food should be given in a concentration to provide 20 calories to one fluid oz.; sweetened condensed milk (1 in 5 by volume) is well tolerated if breast milk is not available, and can be changed to dried milk at a later stage. Within two or three days of starting treatment the full caloric needs should, if possible, be given, perhaps in six feeds in twenty-four hours. If feeds are vomited the author prefers not to repeat them. The eumydrin (1 in 10,000 in water) should be given half an hour before each feed, beginning with 0·5 to 1 c.c. and increasing by 0·5 c.c. at each feed to 2·5 or 3 c.c., and higher if necessary. No gastric lavage is necessary. It is probable that nearly all cases will respond to this regime. If, however, it fails and it is decided to adopt surgical treatment, it would be wise to omit the drug twenty-four hours before operation. In any case, toxic symptoms particularly abdominal distension, indicate a reduction of dosage; often the omission of one dose is all that is required. For distension a reduction of food may also be necessary. How long it is necessary to continue the drug is uncertain, but if it be reduced gradually, 0·5 c.c. at a time, there is little risk of an acute return of vomiting.

With such a routine it is clear that a cooperative mother, who is accurate and methodical, can certainly carry out the treatment at home under supervision. She needs to be instructed in careful measuring and in symptoms of overdosage, and, if her supply of breast milk is liberal, it may be better, though probably not essential, to teach her to express her milk in order to give the baby at first a measured quantity. Whatever the method of treatment employed in

hypertrophic pyloric stenosis, the results obtained must in part depend on familiarity with the method employed and its pitfalls, and in part the avoidance of the risks of cross-infection.

Summary

Forty consecutive cases of hypertrophic pyloric stenosis have been treated with eumydrin with a mortality of 12·5 per cent.; thirty-one cases were cured by eumydrin and four more by operation. Of the five deaths, four were due wholly or in part to enteritis contracted in hospital, and one was probably due to excessive fluid administration. Thirty-five babies showed disappearance of, or reduction in, obstruction at the pylorus after eumydrin treatment. Of the five which showed no response, all had a high fluid intake which was probably the factor which prevented the drug bringing about relaxation of the pyloric spasm. Excessive fluid intake was accompanied by a less rapid response to eumydrin, a slower gain in weight, and often by poor appetite. There was no evidence of benefit from routine gastric lavage. In those cases cured by eumydrin, vomiting was markedly diminished in an average period of 2·9 days, the babies gained an average of 6·8 oz. in the first week, and 6·9 oz. weekly for the first five weeks. The most serious toxic effect encountered in the series was abdominal distension, but there is no reason to suppose this would prove serious were it treated early by reduction of the drug. The drug was used in aqueous solution given by mouth six times daily. In one case only was it given by lingual application in alcoholic solution, which may prove the better method. It is suggested that temporary relief of the spasm at the pylorus may possibly break a vicious circle. The results here recorded should be capable of much improvement with increased experience of this method of treatment. Whereas a mortality of 25 per cent. is not unusual in this country among babies treated surgically, there has been a mortality of 11·5 per cent. among 122 cases treated with eumydrin reported by four physicians in this country.

A plea is made for the more widespread adoption of eumydrin, which has proved so successful in Scandinavian countries, for the treatment of hypertrophic pyloric stenosis in this country.

Sincere thanks are due to the house physicians who have cooperated in the work, as well as to the sisters and nurses at the Queen's Hospital for Children who, in addition to the anxious work of nursing young babies in hospital, have given much time and care to the record-keeping involved.

Postscript. One baby, the only one in the series still on eumydrin when this paper was finished, has since died at fifteen-and-a-half weeks old. She was twenty-two days old when she started treatment, the third youngest in the series (see page 6) and progressed well. She was the child of a fifteen-year-old unmarried mother who was evacuated. She was suddenly weaned after evacuation, grossly underfed on dairy milk, and was twice taken off eumydrin with return of vomiting. On the second occasion the child was re-admitted, but did not respond to medical treatment.

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OBSERVATIONS ON THE GASTRIC ACIDITY DURING THE FIRST MONTH OF LIFE

BY

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Systematic observations on the gastric acidity throughout the first month of life have been undertaken, as no records of its behaviour during that period have been noted in the literature.

In order to investigate the acidity, the fasting juice of fifty healthy, mature breast-fed infants was withdrawn from the stomach seven hours after a feed, daily for the first ten days of life. Thereafter, from the eleventh to the

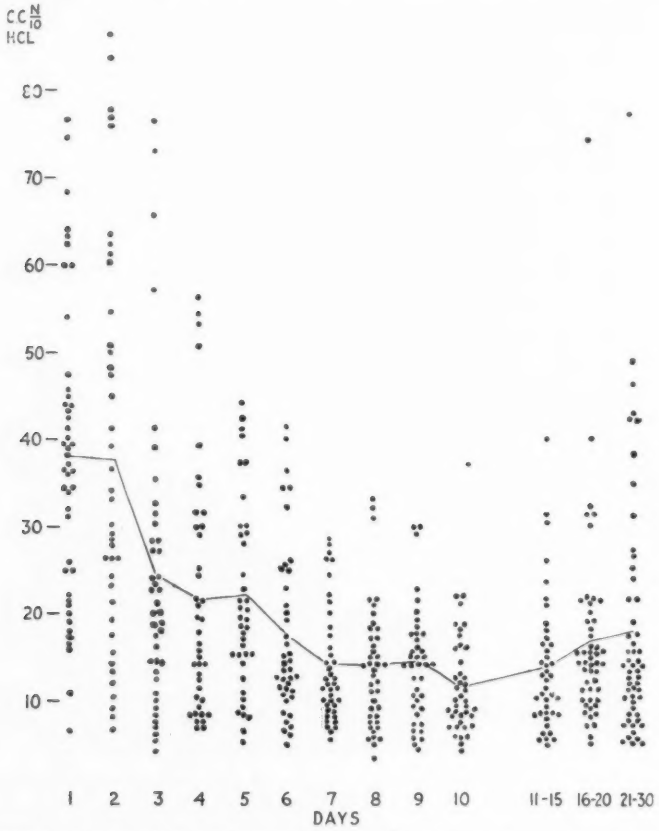

FIG. 1.—The total acidity of the fasting juice during the first month of life, expressed in c.c. N/10 HCl per 100 c.c. stomach contents.

* Working under the auspices of the Kirk Duncanson Research Fellowship of the Royal College of Physicians, Edinburgh.

thirtieth day, the fasting juices were taken from any healthy infant which might be detained in hospital. The following method was used in examining the specimens quantitatively for free and total acidity: 1 c.c. fasting juice when available was titrated with N/70 NaOH and the end points determined with Töpfer's reagent and phenolphthalein respectively. The results are given in fig. 1.

The normal trend of gastric acidity and its causation

The composite figures showing the steady decline of the total acidity of the fasting juice from birth until the tenth day of life give a true impression of the behaviour of each individual infant, particularly when the infant had a high acidity during the first or second day. A similar decline in the gastric acidity after birth has not been recorded in the literature ; but Cutter (1938), after reviewing gastric acidity during the first four years of life and making a few observations himself, suggests that there is probably a fall in the acidity of the gastric secretion after the tenth day of life.

TABLE 1

CASE	DAY	FASTING JUICE	1 HOUR AFTER FOOD	1½ HOURS AFTER FOOD	BODY WEIGHT LB. OZ.
I	2	70·7	45·7	53·6	6 10
	3	25·0	17·4	8·6	6 10
	4	11·4*	14·6	9·7	6 14
	5	14·3	18·6	38·6	7 0
	6	11·4	17·4	16·6	7 0½
	7	7·2	25·0	—	7 1
	10	4·3	10·7	—	7 1½
	14	10·0	14·3	—	7 9
II	2	35·7	28·6	37·7	7 3
	3	18·5	15·6	9·1	7 3
	4	11·4	14·6	12·9	7 1
	5	10/0	9·0	19·3	7 1
	6	9·6	11·4	—	7 0½
	7	7·1	17·1	—	7 2
	10	10·0	12·9	—	7 3
	14	7·1	22·9	—	7 4½
III	2	60·6	55·7	40·0	6 2½
	3	21·1	15·0	14·3	—
	4	15·6	16·6	10·0	6 2½
	5	7·1	21·4	14·6	6 5
	6	11·4	24·6	—	6 7
	7	7·1	6·4*	—	6 6
	10	8·6	17·9	—	6 8½
	14	17·1	35·7	—	—

* Blood present

The most likely explanation of this initial fall in acidity is that some gastrogenic hormone is supplied to the infant in utero, either from the mother or the placenta. The influence of this assumed secretogogue upon the infant is most marked during its first two days. Then it rapidly vanishes, leaving the infant to control its own gastric digestion on or before the tenth day of life. After the tenth day the gastric acidity slowly increases throughout the remaining

days of the first month, but does not attain such a high level as during the first five days after birth. From this fact, it might be assumed that during the first month the infant's digestion is best when it is under six days old. In an attempt to confirm this, three newborn infants were given eight test-meals during their first two weeks. The test-meal consisted of equal parts of breast-milk and water, and amounted to 60 minims per pound body weight. The results are shown in table 1. They express in c.c. N/10 HCl the total acidity in 100 c.c. gastric contents. In table 1, the test-meals show that the reaction of the gastric secretion to the feed is as was anticipated, i.e. the lower the acidity of the fasting juice the poorer was response of the gastric secretion to a test-meal.

The normal daily range of gastric acidity

The difference between the maximum and minimum limit of total acidity gradually decreases with age, until, on the tenth day, it is only 18 c.c. N/10 HCl. This is due to the fact that infants start life with a varying degree of reserve in their gastric secreting power which is probably completely exhausted by the tenth day. Thereafter, the infant exerts its own influence over gastric digestion so as to maintain the basic level for gastric acidity, and later to increase it.

There is at first great variation between the maximum and minimum amounts of free acidity, but after the second day of life the free acidity falls to zero in most cases. The average free acidity is about 20 c.c. less than the average total acidity, as will be seen in table 2, where the acidity is expressed in c.c. N/10 HCl per 100 c.c. gastric contents.

TABLE 2

DAY	NO. OF CASES	FREE ACID	TOTAL ACID
1	45	17·2	38·0
2	40	15·4	37·9
3	41	4·5	24·6
4	40	1·0	21·7
5	40	0·7	22·3
6	40	0·2	17·6
7	40	0·4	14·2
8	41	0·0	14·2
9	40	0·0	14·4
10	40	0·0	11·7
11–15	41	0·7	13·8
16–20	50	1·0	16·9
21–30	45	2·1	18·0

Day of maximum acidity

The maximum acidity in the fasting juice is probably reached within twenty-four hours of birth. In some instances, however, the maximum was reached on the second day. This was due to the fact that the fasting juice was taken so soon after birth that the flow of gastric secretion had not been given time to reach its maximum. Therefore, the maximum average free and total acidity quoted on the first day of life as 17·2 c.c. and 38·0 c.c. respectively is an underestimation. Partly to eliminate this error, the average maximum acidity was calculated

using the highest reading for each infant during the first forty-eight hours. The figures thus obtained are 21·6 c.c. N/10 HCl free acidity and 45·9 c.c. N/10 HCl total acidity. This degree of acidity is astonishingly high, for it is equivalent to that of a healthy adult, and does not reappear in childhood until the age of three years (Levinson and MacFate, 1937). To explain the phenomenon it is necessary to compare the infant's gastric acidity with that of its mother at the time of delivery. Unfortunately, this is extremely difficult because the mother's gastric residue almost always contains bile and occasionally blood, and it is also probable that the mental and physical strain during labour disturbs the normal gastric secretion. However, from observations made by Strauss and Castle (1932) on twenty-four women during their pregnancy and after parturition, it can be concluded that the mother's gastric acidity rises towards normal adult figures at the time of delivery. This is substantiated by Krahmer-Peterson (1939), who stated that the gastric secretion, subnormal during pregnancy, actually returns to the normal adult concentration in almost all cases within a few weeks after parturition. Thus it may be concluded that it is possible for the gastric acidity of the infant to bear a very close relationship to that of the mother at birth.

Achlorhydria in the newborn

The relationship between the mother's gastric secretion and her infant's at birth is further emphasized by the fact that the percentage of mothers with achlorhydria during pregnancy is identical with the number found in mature infants at birth. Achlorhydria was present in three out of twenty-four mothers (Strauss and Castle, 1932), and in six out of fifty infants during the present investigations. These findings are of interest as Faber (1927), after reviewing the question of achlorhydria in children, did not believe that congenital achlorhydria existed, a view shared by the majority of investigators (Tangl, 1906; Hess, 1913; Griswald et al., 1925; and Pollitzer, 1921), who believed that free acid was always present in the fasting juice of the unfed infant at birth.

Correlation of weight progress with gastric acidity

The relationship between the gastric acidity and weight progress of the infant was studied in the fifty infants during the first ten days of life, and there was found to be no connexion between the two at any stage of development. This suggests that it is not essential for infants to have a high gastric acidity in order to maintain their weight and health; that the variable high acidity at birth is merely a provision of nature to maintain an adequate digestive mechanism from birth until the infant's own power of digestion is sufficiently developed. On the other hand, a low gastric acidity does not mean that the infant's digestive powers are subnormal, for the infant in such circumstances can remain in good health and gain weight normally.

The volume and character of the specimens obtained

Out of the 707 specimens tested 73 had to be rejected because they contained either bile, blood or milk. The presence of these substances did not

indicate that disease was present, nor did it mean that there was a delay in emptying of the stomach. In some instances, in which milk was found, the infant had been accidentally fed a short time before the fasting specimen had been obtained.

The amount of fasting juice bore a close relationship to the degree of acidity in that, during the first two days of life when the acidity was highest, the volume was at least 1 to 3 c.c., whereas during the remaining part of the month when the acidity was lower the volume decreased to 0·5 c.c. or less. This can be explained by the fact that the degree of acidity normally varies directly as the rate of secretion (Ihre, 1939). Nevertheless, the amount of gastric residue is partly dependent upon the motility of the stomach, which may conceivably vary during the first month of life. If this is so, it is unlikely that it is responsible for the large amounts of fasting juice during the first forty-eight hours of life, provided the following statement made by Davidsohn (1921) is correct; 'the motility of stomachs in infancy increases or diminishes as the gastric acidity rises or falls.'

Discussion

There seems to be an extrinsic factor, an intrinsic factor, or a combination of both responsible for the fluctuation of the gastric acidity during the first month of life. If it is extrinsic in origin it may be supplied to the infant from the maternal circulation in utero, or in its food after birth. The latter source of a gastrogenic substance is unlikely, for human milk and cow's milk have been tested for hormones by Block (1936) and also by Weisman et al. (1935) with negative results. The chemical constituents of the diet may possibly be responsible for the decline in the gastric acidity, but this is improbable because, after the third day of life, the infant as a rule has an adequate supply of normal food constituents to prevent a fall in the gastric acidity until the tenth day of life. Further, Nicol and Lyall (1939) have shown by numerous experiments, supported by others performed by other investigators, that when man is given a salt-deficient diet, and when the gastric secretion is continuously aspirated, there is no reduction in the sodium chloride or hydrochloric acid content of the gastric secretion.

The probable source of the gastrogenic substance or hormone is either the mother, through the placental circulation, or the placenta itself. Such a suggestion is not fantastic, for Ivy and Farrel (1925) as well as Lim and Necheles (1926) have convincingly demonstrated the existence of a gastric hormone in the blood of dogs, which has been shown to act on the cells of the gastric mucosa producing gastric juice.

Correlation of birth weight with the gastric acidity and the development of the gastric mucosa at birth

From the literature on the gastric acidity in infancy it is clear that almost all unfed infants have at birth free acid in their gastric secretion (Tangl, 1906; Hess, 1913; Pollitzer, 1921; and Griswald et al., 1925). The majority of the investigators did not make quantitative analyses, nor did they contrast the

gastric secretion of the mature infant with that of the premature infant. It was therefore decided to make a comparison of the birth weight with the gastric secretion.

For this purpose the fasting juice was obtained from sixty-three mature infants and sixty-four premature infants within eight hours of birth and before they were fed. The specimens were tested for hydrochloric acid with Gunzburg's reagent, and if it was present, the free acidity was estimated by titrating it with N/70 NaOH, using Töpfer's reagent as indicator. The results are shown in fig. 2, where the acidity is expressed in c.c. N/10 HCl per 100 c.c. gastric juice.

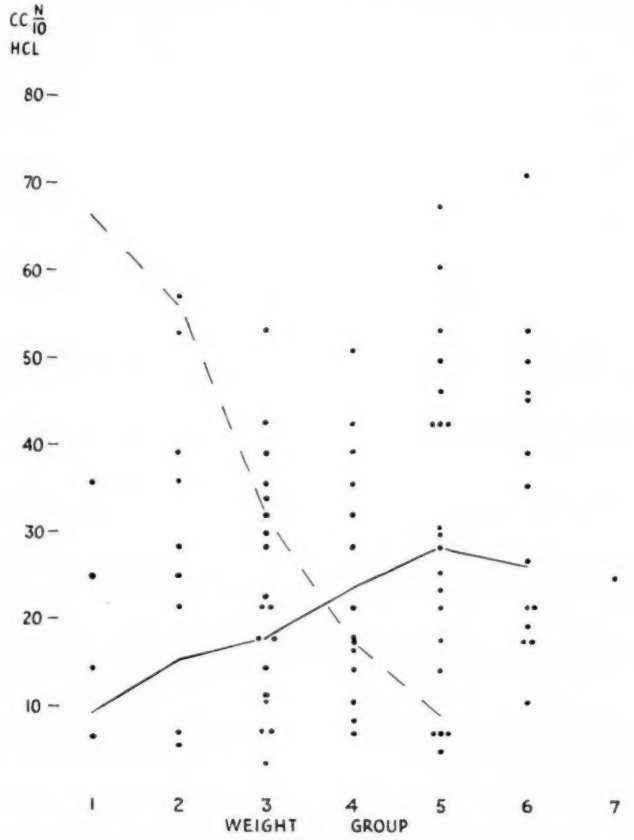

FIG. 2.—To show the effect of increase in birth weight upon the free acidity of the fasting juice. A continuous line demonstrates the average acidity for each weight group. The interrupted line represents the percentage of infants in each group with achlorhydria.

GROUP	NO. OF CASES
1. Under 4 lb. 9 oz.	9
2. 4 lb. 9 oz. to 5 lb.	16
3. 5 lb. 1 oz. to 5½ lb.	24
4. 5 lb. 9 oz. to 6½ lb.	17
5. 6 lb. 9 oz. to 7½ lb.	22
6. Over 7½ lb.	18
7. Average adult	

It will be observed that only eighty specimens are recorded in fig. 2 out of the 127 tested. This is owing to the fact that twenty-seven normal infants had an

achlorhydria at birth and are therefore only represented by the interrupted line. The remaining twenty cases have been omitted because they were suffering from birth injury or disease such as asphyxia or cerebral haemorrhage or because their fasting juice contained bile or blood.

Histological examination of gastric mucous membrane

The state of development of the gastric mucosa was considered, since it was thought that it might explain the varying concentrations of the gastric acidity at birth and the rate of progress of the newborn infant. For this purpose ten stomachs were obtained from infants who died half an hour to eight days after birth. The infants' weights at birth were : 2 lb. 6 oz., 2 lb. 14 oz., 4 lb., 4 lb. 7 oz., 4 lb. 12 oz., 5 lb. 8 oz., 5 lb. 10 oz., 6 lb. 5½ oz., 7 lb. 4 oz., and 7 lb. 8 oz. The stomachs were fixed in formol-saline within half an hour of death, and afterwards sections were taken from the cardio-oesophageal junction, the fundus, the body and the pylorus. The sections were stained with haematoxylin and eosin; and an additional section of the fundus and the body was stained with methylene blue and eosin in order that the oxyntic cells might be seen more distinctly.

The microscopic findings were that in the three smallest infants the stomach mucous membrane was of a very primitive type; the glands were very shallow and loosely packed, and in the region of the fundus and body of the stomach, there were only a few oxyntic cells confined to the base of the glands (fig. 3).

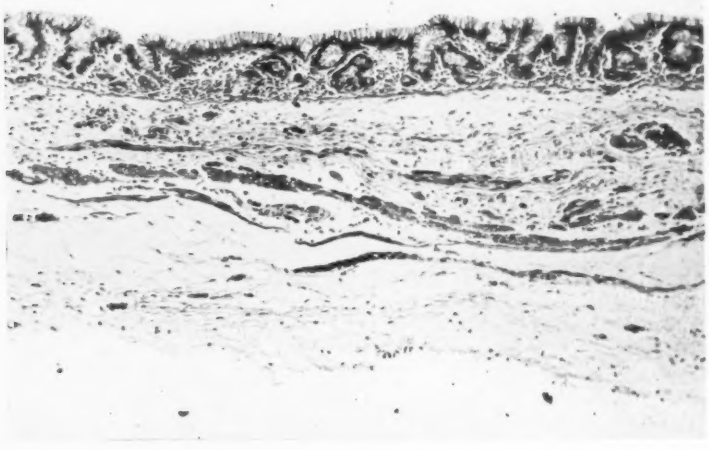

FIG. 3.—Microphotograph of fundus of stomach of infant 2 lb. 6 oz. (×70).

Stomachs from infants of 4 lb. 7 oz. or more had well-developed glands with more numerous oxyntic cells, but these cells did not attain their maximum numbers until the infant's weight was 6 lb. 5 oz. or more. The oxyntic cells were then seen in the body of the glands as well as at their bases (fig. 4). There

FIG. 4.—Microphotograph of fundus of stomach of infant 6 lb. 5½ oz. (×70).

was, however, one stomach, belonging to the infant weighing 5 lb. 8 oz., which did not conform to the general finding that the heavier an infant is at birth the better is its gastric mucosa developed, for it was hypoplastic.

Comment

THE INFLUENCE OF BIRTH WEIGHT. The biochemical and histological investigations show beyond doubt that the heavier an infant is at birth the more likely is it to have a more perfectly developed gastric mucous membrane and potent gastric secretion.

INCIDENCE OF ACHLORHYDRIA AND ITS CAUSATION. Contrary to the findings reported in the literature, achlorhydria in this series of cases occurred frequently, particularly with lower birth weights. It was also noted in ten out of thirteen infants suffering from cerebral haemorrhage. The occurrence of achlorhydria in the latter is not altogether surprising since diminution in the gastric secretion is associated with nutritional diseases, generalized infections and persistent vomiting (Stewart, 1937; Parsons, 1924, 1929; Salmi, 1937; and Steimann, 1936). A possible explanation of hypochlorhydria in the healthy infant is given by finding histologically one mature infant with a primitive gastric mucosa, and progressively more often with the fall in birth weight. Whether the hypoplasia tends to persist in the mature infants and results in the production of congenital achlorhydria is a matter for investigation.

Summary

1. Seven hundred and seven fasting juices were obtained from infants during the first month of life and tested for free and total acidity. The results are

recorded and the average figures throughout the month have been given. From them it is clear that the gastric acidity falls during the first ten days of life and that thereafter it gradually rises. An explanation of this behaviour is discussed and it is suggested that there is a gastrogenic hormone transmitted from the the mother to the infant through the placental circulation. The incidence and causation of achlorhydria is mentioned and discussed.

2. Proof is given that the birth weight of the infant bears a close relationship to the amount of acid secreted by the stomach and to the degree of development of the gastric mucosa. For this purpose fasting juices from sixty-three mature infants and sixty-four premature infants were tested quantitatively for free acid. For the histological examination of the gastric mucosa, six stomachs from premature infants and four from mature infants were used. The specimens were carefully placed in fixative within half an hour of death and sections prepared later in the usual way.

Thanks are due to Professor Charles McNeil for his guidance and the close interest he has given in this work. Thanks are also due to Professor R. W. Johnstone, Dr. W. F. T. Haultain, and Dr. Douglas Miller for permission to carry out the investigations in their wards; and to Dr. Agnes MacGregor for assistance in the histological investigations; and especially to Sister Taylor and the nursing staff for their co-operation in obtaining all the specimens.

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A COMPARISON OF BREAST-FEEDING IN TEN CLASSES OF THE POPULATION

BY

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In a previous paper (Robinson, 1939) it was shown that, though the breast-feeding rate in Liverpool from 1918 to 1937 had not actually declined, it varied from year to year without any apparent reason. In an endeavour to find a possible cause for this I decided to examine the records of all the babies born between January 1, 1930, and May 31, 1940, to group them according to the occupation of the father, and to determine the breast-feeding rate for each group. A difference in the figures thus obtained might account for the fluctuations noted. The cases were limited to those attending the clinic at Norris Green New Housing Estate, Liverpool. A total of 6943 records was collected. Out of these, 5838 were complete. The remaining 1105 were discarded, as 1075 infants ceased attendance while still on the breast, and in thirty cases the occupation of the father was not stated.

It can be seen in table 1 that during the first month the wives of civil servants wean 9 per cent. more babies than do those of labourers and clerks. In the second and third months the weaning rate is highest amongst the semi-skilled and the unemployed classes, whereas it is lowest in the motor-driver class. Between the beginning of the fourth and the end of the seventh month it is low in all classes, and varies by 3 per cent. only. At the eighth month wives of skilled workers and labourers form the greatest number of nursing mothers and those of civil servants the least. The professional group is so small that it may be ignored.

The large numbers contained in the groups of unemployed, skilled workers and labourers made it possible to calculate in each group the yearly weaning rate for ten consecutive years (1930 to 1939). A further thirty-three cases had to be added in order to bring the figure for 1939 up to the total birth rate for this year. The figure for each year includes only the babies born during that year, and the age of weaning is taken from the date of the first supplementary bottle, as in the previous paper. As 1931 contained only ninety-three and 1930 only sixty-four births among unemployed parents, they are both given together under the heading 1931.

Table 2 shows that when these groups are analysed separately a decline in breast-feeding takes place in all, but the variation from year to year still remains.

TABLE 1

GROUP	TOTAL	NUMBER UTILIZED	NUMBER DISCARDED	PERCENTAGE WEANED			
				1ST MONTH	2ND AND 3RD MONTH	4TH TO 7TH MONTH	8TH MONTH AND OVER
Professional * ..	71	56	15	36	25	14	25
Clerks	760	662	98	31	27	16	26
Civil servants ..	247	202	45	39	26	15	20
Services	347	311	36	34	24	16	26
Skilled workers	1435	1227	208	34	23	14	29
Labourers ..	1648	1346	302	31	26	14	29
Motor drivers ..	478	390	88	37	22	13	28
Unemployed ..	1456	1216	240	36	29	14	21
Semi-skilled ..	296	255	41	35	29	13	23
Shopkeepers ..	205	173	32	32	24	16	28
Total	6943	5838	1105				

* Includes male nurses and school teachers.

The percentage of babies weaned in different class groups by the end of the first, third and seventh months; also the number in each group still on the breast at the end of eight months. The numbers utilized and discarded in each group and the total number of case sheets obtained are included.

TABLE 2

DURATION	GROUP	1930	1931	1932	1933	1934	1935	1936	1937	1938	1939
1st month	Unemployed	—	41	33	32	36	32	36	33	35	52
	Labourer ..	20	25	24	27	26	28	41	39	36	47
	Skilled worker	30	27	26	27	29	43	37	37	40	39
2nd and 3rd months	Unemployed	—	23	25	27	29	32	34	37	35	26
	Labourer ..	23	20	24	21	33	26	28	28	32	27
	Skilled worker	19	20	21	25	22	22	22	27	29	28
4th to 7th months	Unemployed	—	12	10	15	12	18	18	12	15	12
	Labourer ..	16	13	10	16	11	14	16	14	18	11
	Skilled worker	16	18	11	16	17	13	20	10	11	9
8 months and over	Unemployed	—	24	32	26	23	18	12	26	15	11
	Labourer ..	41	42	42	36	30	32	15	19	14	15
	Skilled worker	39	35	42	32	32	22	21	26	20	24
Numbers utilized	Unemployed	(64)	157	113	118	174	148	139	145	127	101
	Labourer ..	174	138	147	128	141	113	123	134	114	116
	Skilled worker	138	106	136	104	129	121	121	129	105	107

The percentage of three social classes of babies weaned in each of the ten years under consideration is given for the end of the first month, third month and seventh month. Also the number still being fed at the end of the eighth month. The total number utilized in each year and group is given at the foot of the table.

It is interesting to note that the lowest number in the unemployed group occurs in 1930, and is followed two years later (1932) by the highest breast-feeding rate in all groups at eight months; whereas the highest number in the unemployed group occurs in 1934, and is followed two years later (1936) by the lowest breast-feeding rate in all groups at eight months. A similar result is produced during the fourth to seventh month, but the earlier months are apparently unaffected. If the number receiving help from the Unemployment Assistance Board and Public Assistance Committee may be taken as a rough index of the state of unemployment in the community as a whole, it may be concluded that economic factors do not directly affect the ability to breast-feed but have a remote effect on the duration of suckling only after the baby is three months old. Recently, several mothers have asked me why it is that they fed their first child (now about eighteen months to three years old) when they were poorly fed, owing to their husbands being out of work, and now, when their husbands are earning good money and they are better fed and getting one pint of milk daily, they cannot feed their second infant more than three months without supplementary feeds. It may be that their store of some material essential to breast-feeding was exhausted during the feeding of the first child while on a deficient diet, and that the present diet, increased as it is by animal protein, vegetables and milk, does not provide enough essential food to replace that which has been lost.

Table 2 shows also that the yield of breast-milk in the first month is diminished among the wives of the unemployed, since in this group the highest percentage of infants weaned occurs during this period in each year of the decade under consideration. This inability to lactate may be due to prolonged under-feeding, but, unfortunately, the duration of unemployment is not recorded. It varied from repeated short periods to a continuous stretch of at least ten years. For some unknown reason the weaning rate amongst the wives of skilled workers increased in 1935 to almost the same level as that of the wives of the unemployed, and a year later a similar rise occurred in that of the wives of labourers, and in both cases continued thereafter at this higher rate.

In the light of the above observations it will be interesting to watch the effect of the present fall in unemployment, and of the new milk scheme just started by the Government.

Summary

The records kept at the Infant Welfare Centre, Norris Green, Liverpool, since the beginning of 1930 were examined and divided into social groups. The weaning rate of each group was calculated and comparisons were made. The three largest classes were each subdivided into groups containing the babies born in every consecutive year for ten years. The weaning rate was calculated and the results were compared.

Conclusions

(1) There is no real decline in breast-feeding when all classes are considered together over a long period.

(2) Each class has a weaning rate of its own, but the differences between them is not marked.

(3) During the ten consecutive years (1930 to 1939) there is a real decline in breast-feeding in three social groups. The greatest decline occurs in the first month among the wives of labourers.

(4) Variations in prosperity have not an immediate but a remote effect on breast-feeding, appearing only after two years and limited to the later months.

(5) Continued poverty lowers the ability of the mothers to keep the baby on the breast throughout the first month.

Thanks are due to Dr. W. M. Frazer, Medical Officer of Health for the City of Liverpool, and to Dr. R. E. Bell, Senior Assistant Medical Officer in charge of the Maternity and Child Welfare Department, City of Liverpool, for permission to publish this work.

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The following seven papers from the Resident Staff of the Hospital for Sick Children, Toronto, were presented at a regular staff meeting at the hospital in 1940. Professor Alan Brown suggested their publication in the 'Archives of Disease in Childhood,' and the Editors gladly assented.

A LABORATORY INVESTIGATION OF PNEUMONIA AMONG INFANTS AND CHILDREN

BY

W. J. AUGER, M.D.*

With the technical assistance of ISABEL SCOTT, B.A.

The results of sputum examinations from 450 cases of pneumonia in infants and children covering a nine-month period from September 8, 1938, to June 8, 1939, were reported previously (Auger, 1939a). These results were characterized by numerous cases of empyema due to type I pneumococcus and many deaths. During the past pneumonia season from September 8, 1939, to April 18, 1940, a seven-month period, 450 cases have again been examined, but in these there was a low mortality rate and few cases of empyema. Evidently 1939–40 must be regarded as a mild season as compared with 1938–39, which constituted a severe season. In view of this apparent seasonal variation in pneumonia incidence and virulence a careful study and comparison has been made of the statistics for the two seasons from an etiological point of view. These results have been tabulated and interpreted graphically to show the most interesting and salient features.

The method used for examining and culturing sputum is unique. In most of the cases the sputum has been obtained from the nasopharynx. We believe that a nasopharyngitis always precedes pneumonia in children and that the best means of studying the bacteriology of an early case of pneumonia in a child is to study secretions from the nasopharynx. In cases of late pneumonia, whooping cough, or tuberculosis, laryngeal sputum is better suited to examination. The sputum is obtained by suction (Auger, 1939b) from the nasopharynx and a tentative report is made on examination of the direct smear. Sputum from the nasopharynx is ideal in this respect since it is relatively free from mouth organisms which are so easily confused with pneumococci. The sputum is then typed by the Neufeld method if pneumococci are present in the direct smear. The sputum is then cultured on a blood agar plate which is incubated in the presence of moist carbon dioxide (Auger, 1939c). The injection of mice is no longer considered necessary for the isolation of pneumococci in our laboratory.

* Working under a grant from the Banting Research Foundation in the Department of Pathology and Bacteriology at the Hospital for Sick Children, Toronto.

The pneumonia cases are all those reported to the laboratory with positive chest findings and checked in most instances by a positive roentgenogram and by a member of the attending staff. No distinction has been made between lobar- and broncho-pneumonia. The two conditions were never distinguishable on a basis of sputum examination. These cases have not been subdivided into primary or secondary pneumonia except in the mortality table, since the etiological cause at the onset of the pneumonia in children is of most interest and is likely to be the same whether the child has a congenital heart or a normal constitution. On the other hand, an underlying ailment may greatly influence the prognosis.

In fig. 1 is shown the monthly incidence of pneumonia cases and deaths for the past three years. The case incidence for all types of pneumonia is shown by

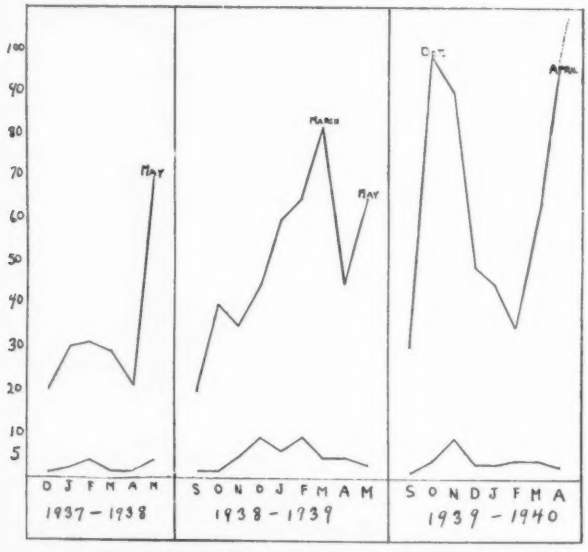

FIG. 1.—Graphic representation of monthly incidence of pneumonia cases and deaths for three pneumonia seasons. The upper line represents the number of cases and the lower line the deaths following primary pneumonia.

the upper line and the number of deaths following primary pneumonia by the lower line. The definition accepted of primary pneumonia is one in which the onset or progress is not influenced by any concurrent disease. The vertical coordinate gives the actual number of cases while the horizontal coordinate the first letter of the month.

In the first section are shown the statistics for 1937–38. These are incomplete, since the pneumonia study had just been begun; they are shown to emphasize the fact that a striking rise in case incidence without any corresponding rise in fatalities occurred in May. May is a spring month not usually associated with pneumonia.

In the second section are shown the curves for 1938–39 or the severe pneumonia season. Here it is seen that the case incidence forms a peak during the winter months of January, February, and March and again in May. The corresponding mortality curve roughly follows the case incidence curve, with a

crest during December, January, and February. It is interesting to note again that this curve falls away in May in spite of the corresponding sharp rise in case incidence.

In the third section are shown similar curves for 1939–40 or the mild season. Here the peak of case incidence is in October and November of 1939 and again in April, 1940. It is likely that the month of May will show a still higher case incidence, since there was an average of eight to twelve cases of pneumonia per day during the last two weeks before this paper was completed. It is most interesting to note that the curve of case incidence is a valley during the winter months of December, January, February, and March, or the reverse of the 1938–39 or severe pneumonia season. The mortality curve roughly follows the course of the incidence with its peak in November. However, it may be noted that the mortality curve significantly drops in April in spite of the rise in incidence. Evidently April and May can be severe months as to case incidence but are mild as to pneumonia virulence. From these curves it was judged that a severe pneumonia season among infants and children in Toronto is associated with a rise in case incidence during the winter months and a less severe or mild season with a low winter case incidence.

TABLE I

SHOWING MORTALITY ACCORDING TO AGE FROM SEPT. 8, 1938, TO JUNE 8, 1939, AND FROM SEPT. 8, 1939, TO APRIL 19, 1940

AGE	1938–1939		1939–1940	
	CASES	DIED (PER CENT.)	CASES	DIED (PER CENT.)
0–1 year	121	27·5	109	18·3
1–2 years	67	6·7	79	12·1
2 years	262	5·5	262	2·5
Total	450	10·5	450	7·1

In table 1 the mortality figures for the mild and severe pneumonia seasons are compared. These figures are based on statistics from 450 pneumonia cases among infants and children from September 8, 1938, to June 8, 1939, and September 8, 1939, to April 19, 1940. Only the deaths following primary pneumonia have been recorded. In about 80 per cent. of the deaths the lungs were examined culturally either at post mortem or by lung aspiration. When there was failure to obtain a post-mortem examination the case was judged to be a primary pneumonia on the basis of history and sputum examination. The cases have been classified according to age: up to one year, one to two years, and over two years. The mortality is seen to be highest for both seasons in infants under one year of age and is lowest in the over-two-years age group. A marked decrease in mortality is noted during the 1939–40 season. There is an exception in the one-to-two years age group, which possibly can be explained

on statistical variation, since there are many fewer cases. It should be pointed out that most of the pneumonia cases are in the over-two-years age group and it is here that the mortality and incidence of empyema are significant. The mortality was less than one half during the mild than in the severe season and a corresponding reduction in number of empyemas will later be shown.

Table 2 shows the incidence of the common pathogenic bacteria found in sputum from 450 cases of pneumonia from September 8, 1939, to April 19, 1940. These figures are remarkable in their similarity to the figures reported in a similar table for 1938–39. Practically all of these figures represent single specimens of sputum from the patient on admission to hospital. The cultures from lungs, blood cultures and pleural fluids agreed with the results of the sputum examinations in early pneumonia in about 90 per cent. of the cases.

TABLE 2
SHOWING INCIDENCE OF PATHOGENIC ORGANISMS IN PNEUMONIA SPUTA FROM SEPTEMBER 8, 1939, UNTIL APRIL 19, 1940

AGE	NO. OF CASES	PNEUMO-COCCUS	MORE THAN ONE TYPE	MORE THAN ONE PATHOGEN	STREP. HAEM.	H. INFLU-ENZAE	STAPH. AUREUS	OTHERS
Under 2 years.	184	131	14	23	19	13	42	15
Over 2 years.	266	222	32	25	25	17	24	7
Total ..	450	353	46	48	44	30	66	22
Per cent.		78·4		10·7	9·8	6·7	12·4	4·9

Forty-six or 13 per cent. of the 353 sputa with pneumococci present contained two types, and in two instances three types, in the same sputum. This multiplicity of types may be very confusing in infants in whom the common virulent pathogens such as I, II, or V are uncommon. Two types of pneumococci in the same sputum usually indicate a severe case of pneumonia. Also included is a column for the cases with more than one pathogen in the same sputum, which amounted to 10·7 per cent. In many of these cases it is extremely difficult to know whether the pneumococci or the coincident pathogen or both is the cause of the pneumonia. Probably the pneumococci should receive preference in the initial stages, whereas the other pathogen should receive more consideration in the later stages of the pneumonia. This is particularly true for cases which are not responding to chemotherapy. In the other columns is recorded the incidence of other pathogenic bacteria when occurring in sufficient numbers to be recorded. The streptococcus haemolyticus has decreased from 22 per cent. for 1938–39 to 9 per cent. for the past winter. This striking reduction in the incidence of streptococcus haemolyticus in the sputum will be reflected in the empyema table. The column dealing with staphylococcus aureus has been transferred to table III. In the last column it is seen that only 4·9 per cent. of the pneumonia cases did not contain definite etiological bacteria in their sputa. Most of these were ' late ' cases of pneumonia probably receiving some specific therapy at home.

TABLE 3

SHOWING INCIDENCE OF STAPHYLOCOCCUS AUREUS IN SPUTUM AND LUNGS AFTER DEATH ACCORDING TO AGE GROUP FROM SEPTEMBER 8, 1938, TO JUNE 8, 1939 AND SEPTEMBER 8, 1939, TO APRIL 19, 1940

AGE	1938–39		1939–40	
	INCIDENCE OF STAPH. AUR. IN SPUTUM	DEATHS WITH STAPH. AUR. IN LUNGS (PER CENT.)	INCIDENCE OF STAPH. AUR. IN SPUTUM	DEATHS WITH STAPH. AUR. IN LUNGS (PER CENT.)
Under 2 years ..	49	32·7	42	23·8
Over 2 years ..	22	9·0	24	0

Last year we reported a disproportion in the incidence of staphylococcus aureus in sputum of infants as compared with children over two years of age, and a correspondingly high incidence in the lungs of infants under one year of age at death. During the 1939–40 season a similar disproportion has been observed and table 3 was drawn up to direct further attention to this fact. Staphylococcus aureus in sputum from the nasopharynx was only recorded when it was judged to be in sufficient amount in the direct smear and blood agar plate to be a likely etiological factor. The lung cultures were obtained only from cases of primary pneumonia. In many of these lung cultures (about 50 per cent.) other pathogenic bacteria besides the staphylococcus were present. In the table it is seen that in 1938–39, 32 per cent. of infants under two years of age with staphylococcus aureus in their sputum died either partly or solely as a result of this infection. This high incidence was slightly lower for the 1939–40 season, namely 23 per cent. In the over-two-years age group there were fewer cases with staphylococcus in the sputum and also a proportionately smaller death rate; in fact, there were no deaths in the mild season of 1939–40 as a result of this organism. It would appear, then, that staphylococcus aureus in the nasopharyngeal sputum of infants is more serious than in older children. The greatest contribution modern chemotherapy can make to the problem of children's pneumonia is in the reduction of the high mortality in infancy, which is chiefly due not so much to the pneumococcus, as to staphylococcus aureus. The minor rôle of the pneumococcus in the mortality of infants was clearly shown in the table of mortality according to etiological agent in last year's report. Table 4 also suggests that a reduction in mortality due to staphylococcus aureus is partly associated with the mild pneumonia season of 1939–40.

Table 4 shows the incidence of the common or important types of pneumococci occurring singly in sputum for 1939–40. The usual preponderance of higher types of pneumococci in the under-two-years age group is well demonstrated. Attention should be paid to the incidence of type I. There were only forty-one cases or 13 per cent. of type I pneumococci and the corresponding figure for last season was 79 or 28 per cent. This reduction is reflected in the

correspondingly low incidence of type I empyema as shown in table 5. The other common types found in the sputum were VI, XIV, XIX and XXIII, and are similar in their percentage incidence to 1938–39

TABLE 4

INCIDENCE OF IMPORTANT TYPES OF PNEUMOCOCCI OCCURRING SINGLY IN PNEUMONIA SPUTUM FROM SEPTEMBER 8, 1939, TO APRIL 19, 1940

	CASES	TYPES								
		I	II	V	VI	XIV	XV	XIX	XXIII	UTP *
Under 1 year ..	117	4	0	0	16	8	7	14	9	18
Over 2 years ..	190	37	13	16	8	10	6	16	10	18
Total	307	41	13	16	24	18	13	30	19	36
Per cent.		13·3	4·2	5·2	7·8	5·9	4·2	9·8	6·2	11·7

* Untypable pneumococci which were bile soluble.

Table 5 shows the incidence of empyemas for the severe pneumonia season of September 8, 1938, to June 8, 1939, as compared with the mild season of September 8, 1939, to April 19, 1940, according to etiology and age group. These figures include all the cases of empyema in the wards in the intervals stated. The most interesting feature is the fact that there were over four times the number of empyemas during the severe than the mild season. It is next seen that empyemas due to type I pneumococcus and streptococcus haemolyticus show the most profound decrease in incidence during the mild season. It is also noticeable that these cases mostly occur in the over-two-years age group. Staphylococcal empyemas were the same for both seasons and were predominantly in the under-two-years age group. It could be argued that this reduction in empyema incidence is due to the fact that more children were

TABLE 5

SHOWING INCIDENCE OF EMPYEMAS FOR THE SEVERE AND MILD PNEUMONIA SEASON ACCORDING TO ETIOLOGY AND AGE

	TOTAL		TYPE I		OTHER TYPES OF PNEUMO.		STAPH. AUR.		STREP. HAEM.		H. INFLUENZAE		MIXED ORGANISMS	
Season..	S	M	S	M	S	M	S	M	S	M	S	M	S	M
Under 2 years.	10	7	0	1	2	0	5	5	0	1	1	0	2	0
Over 2 years.	44	5	28	3	4	1	1	1	9	0	1	0	2	0
Total	54	12	28	4	6	1	6	6	9	1	2	0	4	0

receiving chemotherapy (chiefly sulphapyridine) during the mild than the severe pneumonia seasons. It is undoubtedly true that more children in the hospital received sulphapyridine during the past winter, but 50 per cent. of cases of empyema include, for both pneumonia seasons, children admitted to the hospital with empyema who probably received inadequate treatment at home. It is hardly likely that the chemotherapy administered at home by the family physician would greatly influence or lower this 50 per cent. portion of the empyema incidence during the mild season.

Table 6 shows the results of specific serum treatment for cases of early type I pneumonia. It can be observed from table 5 that, for the two pneumonia seasons there were altogether 39 cases of pneumococcic empyema, of which 32 or 82 per cent. were due to type I. So that pneumonia in children due to type I pneumococcus is a serious problem and deserves special attention. We reported last year that in a small series of seventy-four early type I pneumonia cases 20 per cent. of the controls developed empyema, 16 per cent. following specific serum therapy and only 8 per cent. following sulphapyridine therapy. This year it was decided to eliminate the controls and concentrate on the lowering of the incidence of empyema. It was also decided to compare the efficacy of sulphapyridine and sulphapyridine plus serum therapy in the prevention of empyema. I am fully aware that it would have been better to have included a control group in light of what has been shown as to seasonal variation in pneumonia virulence. However, the series would have been too small to be of any use if the fifty-three cases had been divided into three groups. As it is, the number of cases in each group is about the same as last season but with the exception that there are no controls. So it was planned to divide the pneumonias into two groups, the first receiving sulphapyridine alone, and the second sulphapyridine plus type I specific anti-pneumococcal rabbit sera, which was given intravenously. The serum was obtained from the Connaught Laboratories, Toronto.

TABLE 6

SHOWING RESULTS OF EARLY TYPE I PNEUMONIA CASES TREATED IN SERIES FROM SEPTEMBER 8, 1939, TO APRIL 19, 1940

	SULPHA-PYRIDINE	SULPHA. AND SERUM	TOTAL
No. of cases . .	27	26	53
Empyema	0	2	2
Percentage of empyema	0	7·7	3·8
Surgical drainage . .	0	2	2
Deaths	0	0	0

It is seen that the incidence of empyema, 3·8 per cent., is far below last year's incidence even for last year's sulphapyridine figure of 8 per cent. Undoubtedly this reduction could not be due solely to early specific therapy. Although the point cannot be proved, we are satisfied that this figure is a minimum and only a passage of years will decide. It is interesting to note that the two cases of

empyema were following serum plus sulphapyridine. It is admitted that these figures are too small to be conclusive.

Discussion

This investigation emphasizes the fact that before pneumonia statistics for any particular year or month can be assessed seasonal variation must be taken into account. This is particularly true for controlled serial investigations such as we have conducted in respect to specific treatment for cases of early type I pneumonia during the past two years. The investigation suggests that seasonal variation both from month to month and year to year in respect to pneumonia incidence and virulence can occur. These fluctuations in pneumonia virulence are most noticeable in the over-two-years age group in which the reduction in empyemas due to type I pneumococcus and streptococcus haemolyticus was most marked. The decrease in mortality was also most apparent in the over-two-years age group. Further investigation of the figures from the point of view of meteorology and the incidence of nasopharyngitis should prove interesting.

Summary

Laboratory investigation of pneumonia in infants and children indicates that the severe pneumonia season of 1938–39 was associated with a rise in case incidence during December, January, February, and March with a high mortality, whereas the mild pneumonia season of 1939–40 was associated with a decrease in incidence and a relatively low fatality rate during these months.

The reduction in mortality was particularly noticeable in the over-two-years age group, in which it was less than half during the mild as compared with the severe pneumonia season.

A study of the etiological bacteria in the sputum for the two pneumonia seasons showed that there was a striking reduction in incidence of type I pneumococcus and streptococcus haemolyticus, which was further borne out by a marked reduction in the incidence of empyemas due to these organisms during the mild season.

Staphylococcus in the sputum of infants under two years of age is of serious portent. The high mortality and incidence of empyema in this age group is relatively unaffected by seasonal variation.

It is concluded that seasonal variation in pneumonia incidence and virulence for childhood pneumonia can occur both from month to month and year to year. This interesting fact deserves more investigation.

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PROGNOSIS AND TREATMENT OF ACUTE DIFFUSE PERITONITIS IN CHILDREN SINCE THE ADVENT OF CHEMOTHERAPEUTIC DRUGS

BY

KENNETH M. ALFORD, M.D.

For the past few years the paediatric and surgical literature has contained numerous articles on methods of treating cases of peritonitis in children in an effort to bring down the high mortality rate. Most of these articles have been specially concerned with peritonitis following acute appendicitis with perforation, and both the conservative school which bases treatment on Ochsner's (1902) original plan and the school which believes in early operation, as described first by Blake (1903), report remarkably low mortality figures. An analysis of all the cases of acute diffuse peritonitis that have come into, or developed in, the medical and surgical wards of the Hospital for Sick Children, Toronto, since 1935 shows an appalling death-rate. Sixty per cent. of cases died. When these deaths are plotted on a graph with each year's mortality rate noted separately, a dramatic drop in the mortality figures appears to have taken place in the past two years. It is the purpose of this paper to analyse these cases of peritonitis and find out in what respects the treatment has been altered so as to bring about this more favourable prognosis.

For the purpose of simplifying the classification of these cases they have been divided into two groups: (1) primary or idiopathic peritonitis, and (2) secondary peritonitis, rather than classified under their respective causative pyogenic organisms. The primary group includes infections extending from the navel in the newborn or sepsis neonatorum involving the peritoneum; infections by the blood stream with organisms carried to the peritoneum from a distant focus such as the throat, ear, lungs, or joints; lymphatic invasion; or infections from the genito-urinary tract. The secondary group includes the intra-abdominal catastrophes with perforation of the bowel as a result of trauma, infection, peptic ulcer, congenital abnormality or the conditions which interfere with the blood supply of the bowel.

With these two main groups in mind, table 1 represents the yearly mortality rate for all cases of diffuse peritonitis that have been admitted to the hospital since 1935. These figures are shown graphically in fig. 1. It is shown that since January 1, 1939, all types of peritonitis, whether primary or secondary, have responded to hospital care much more efficiently than previously, since

they have been given large doses of sulphanilamide and sulphapyridine, depending on the nature of the causative organism.

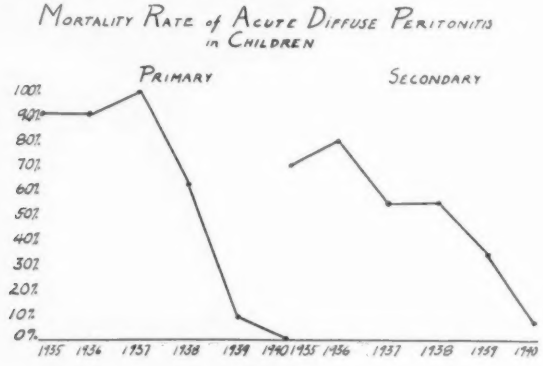

FIG. 1.

TABLE 1

MORTALITY RATE OF ACUTE DIFFUSE PERITONITIS

	PRIMARY			SECONDARY		
YEAR	CASES	DEATHS	PERCENTAGE MORTALITY	CASES	DEATHS	PERCENTAGE MORTALITY
1935	24	22	91·6	20	14	70
1936	12	11	91·6	20	16	80
1937	10	9	100	20	11	55
1938	8	5	62·5	7	4	55
1939	11	1	9	23	8	34·7
1940	2	0	0	13	1	7·6
Total	67	48	71·6	103	54	52·4

For the purpose of discussing treatment, primary peritonitis will be subdivided into streptococcal peritonitis and pneumococcal peritonitis, as these are by far the most common causative organisms (table 2).

TABLE 2

CAUSATIVE ORGANISMS IN PRIMARY PERITONITIS

Haem. streptococcus	41	
Haem. strept. + B. coli	1	
Haem. strept. + staph. aureus	1	
Non-haemolytic streptococcus	1	
Pneumococcus	15	Type I—9 Type II—1 Type VI—1 Types XI and XXIX—1 Not specific types—3
B. coli	1	
Staphylococcus aureus	1	

Primary peritonitis

In determining the type of primary peritonitis from a bacteriological standpoint, only eleven vaginal smears were taken, none of which was positive

for pneumococcus, so that clinically the classical primary pneumococcal peritonitis described by Mechant (1901) could not be diagnosed in this series. There were twenty throat swabs taken, fourteen of which were positive and checked with five positive blood cultures. There were fifty-four blood cultures taken in the group with twenty-nine positive. Peritoneal fluid was obtained and cultured only twenty-nine times while the child was alive and gave the causative organisms in twenty-eight of these cases. Fortunately thirty-one out of forty-eight post-mortem examinations were obtained, so that it was possible not only to check the accuracy of the clinical bacteriological findings but also to determine the type of organism present when the peritoneal fluid was not obtained before death. The importance of obtaining peritoneal fluid, either by inserting the 17-standard wire gauge short bevel needle with a dull point into the peritoneal cavity or by doing a surgical exploration under local anaesthesia, to determine the nature of the offending organism is emphasized here because the result of the finding determines the subsequent method of therapy.

In the cases of streptococcal peritonitis approximately 75 per cent. of the cases were associated with an upper respiratory infection, such as rhinitis, pharyngitis, tonsillitis, otitis media and mastoiditis. The remainder were associated in four instances with erysipelas, one complicating scarlet fever and one measles; one case was associated with nephrosis and one with streptococcal suppurative arthritis and osteomyelitis. In the pneumococcal group it was harder to find an etiological background, but 50 per cent. were associated with upper respiratory infections and the other 50 per cent. could not be determined.

The average age incidence for primary peritonitis was three years and ranged between three-and-a-half hours and eleven years. Twenty-seven of the cases were infants under two years of age and in this group twenty-four died, a mortality rate of 88·8 per cent. The three infants that lived all recovered in the past year on chemotherapeutic drugs. There were a few more female children suffering from this disease than males (56·7 per cent.). The important signs and symptoms were similar in both the pneumococcal and streptococcal varieties of peritonitis. The children suffered from vomiting, abdominal pain and diarrhoea, and in the infant group the mother almost invariably stated that the child had colic, abdominal tenderness and irritability. The temperature on admission averaged 103° F., varying between 97° and 106·2°. The average leucocyte count was 19,000 per c.mm., varying between 3,700 and 138,000; the latter was a case complicated by broncho-pneumonia. The average number of polymorphonuclear granulocytes was 75 per cent., with a variation between 40 per cent. and 98 per cent. On physical examination all the children appeared acutely ill, with considerable amount of abdominal tenderness and distension. In 75 per cent. of the streptococcal and 50 per cent. of the pneumococcal infections other evidence of disease could be found in either the ear, nose, throat, skin, joints or chest.

In discussing the treatment of these cases in relation to the mortality rate it is proposed to start at the beginning of the present series. In 1935, two cases recovered. Both were of the pneumococcal variety. One was a type II

pneumococcus peritonitis who received nothing specific, but recovered after running a stormy course for one month. The other recovery received 60,000 units of type I anti-pneumococcal horse serum intravenously. In 1936 there was one recovery also of pneumococcal type I origin. He recovered on the administration of 260,000 units of anti-pneumococcal horse serum. All in the 1937 series succumbed. One was removed by the parents when acutely ill. Six haemolytic streptococcal and two pneumococcal infections received no specific therapy. Two children received sulphanilamide and died. One was given 15 grains of sulphanilamide before death, which was three hours after being admitted to hospital, and the other received an insufficient dose of sulphanilamide as it is now calculated in accordance with the resulting blood levels. This was during the early experimental stage with these drugs, and prontosil was given intravenously along with the sulphanilamide by mouth, with a resulting deep red pigmentation of the skin and mucous membrane.

In 1938 there were five cases of haemolytic streptococcal infection. Four died. Two of these received no chemotherapy and two who received sulphanilamide were young infants. One, four weeks of age, who received an adequate dose (2 to 3 grains per pound of body weight in twenty-four hours), but was only able to concentrate in the blood up to 1·4 mgm. per cent. A six-weeks-old infant had an insufficient dose of sulphanilamide plus the intravenous administration of prontosil, and showed no response to either drug. One child recovered on 1 grain of sulphanilamide per pound of body weight over a period of two weeks with a blood concentration of 3·9 mgm. per cent. There were also three cases of pneumococcal infection. The one who died had a type VI infection and received no specific therapy. The two who recovered were both due to type I pneumococcus and were given large doses of anti-pneumococcal rabbit serum, and one of the two in addition received sulphanilamide by mouth.

In 1939 there were nine cases of haemolytic streptococcal peritonitis with eight recoveries. Six received adequate doses of sulphanilamide; one started on sulphanilamide, but, as he did not respond, was changed to sulphapyridine and subsequently recovered; and one received sulphapyridine alone. The children on sulphanilamide received $1\frac{1}{2}$–3 grains of the drug per pound of body weight per day from nine to twenty-seven days with an average of 9·3 mgm. per cent. concentration in their blood. The ten-months-old girl on sulphapyridine received 3 grains per pound for eight days and then the dose was cut to $1\frac{1}{2}$ grains per pound for ten days. The boy that died was a case of streptococcal peritonitis who was put on adequate doses of sulphapyridine and soludagenan for eighteen days before sulphanilamide was tried, and then only for twenty-four hours. He was then changed back to soludagenan because of persistent vomiting. He had an average sulphapyridine concentration of 10·1 mgm. per cent. in the blood stream, but went on to develop pneumonia and empyema and finally died. It has been our opinion in the Toronto clinic that children suffering from streptococcal infections do better on sulphanilamide and those from pneumococcal better on sulphapyridine. If this boy were again to come under our care sulphanilamide would have been started at the beginning,

and then if there had been no response sulphapyridine and soludagenan begun. Of four cases of pneumococcal peritonitis who recovered, two of type I received antipneumococcal rabbit serum plus sulphapyridine. A third child with type XI and type XXIX pneumococcus and one with an untypable pneumococcus made good recoveries on adequate doses of sulphapyridine alone. These children received between 1 and 1½ grains sulphapyridine per pound of body weight and maintained an average concentration of 4·4 mgm. in the blood stream.

The present treatment for primary peritonitis in children as a result of our experience with the chemotherapeutic drugs is outlined in table 3.

TABLE 3

PRESENT TREATMENT FOR PRIMARY PERITONITIS IN CHILDREN

1. Obtain peritoneal fluid on admission to determine specific organism.
2. Check above by blood culture, sputum examination (Auger method), and vaginal culture.
3. Fowler's position.
4. Light cradle to abdomen.
5. Continuous intravenous administration of fluids, in infants, 2/3 glucose in distilled water + 1/3 normal saline; older children, 5 to 10 per cent. glucose in normal saline.
6. Type child and have donor ready to give transfusion if haemoglobin or white blood-cells drop following the administration of chemotherapeutic drug, or if serum protein falls following continuous intravenous fluids.
7. For streptococcal infection—sulphanilamide, 2 to 3 grains per lb. body weight in twenty-four hours until the concentration in blood reaches 10 mgm. per cent. and then cut down to 1–1½ grain per lb. body weight until temperature remains normal for two to three days and clinically child is cured.
8. For pneumococcal infections—sulphapyridine, 1 to 2 grains per lb. body weight in twenty-four hours until concentration in blood reaches 4–5 mgm. per cent. and then continue with 1 grain per lb. until temperature remains normal for two to three days and clinically child is improved.

   In addition 100,000–200,000 units of type specific antipneumococcal rabbit serum.

Secondary peritonitis

Secondary peritonitis, classified above, presents chiefly a surgical problem, the most important aspect of which concerns acute appendicitis with perforation, which I do not feel qualified to discuss. The statistics of these cases raised some interesting problems. The mortality rate, as in primary peritonitis, has made an appreciable drop, although more gradually than in the first group (table 4), the best results, obtained in the past year, having followed combined

TABLE 4

MORTALITY RATE COMPARING SECONDARY PERITONITIS WITH APPENDICEAL PERITONITIS

	SECONDARY			APPENDICEAL		
YEAR	CASES	DEATHS	MORTALITY PER CENT.	CASES	DEATHS	MORTALITY PER CENT.
1935	20	14	70	14	9	64
1936	20	16	80	13	10	76
1937	20	11	55	16	7	43
1938	7	4	55	5	2	40
1939	23	8	34·7	19	4	21
1940	13	1	7·6	12	0	0

surgical treatment with the use of chemotherapeutic drugs. This method of treatment has already been reported by Ravdin, Rhoads and Lockwood (1940) who used sulphanilamide in cases of peritonitis following ruptured appendix after they had found in experimental animals that sulphanilamide diffuses readily into the peritoneal fluid. Clinically they found that their recoveries did not run the stormy course which they had done prior to the use of the drug.

The cases of secondary peritonitis in the present series were due to the associated diseases shown in table 5, and the causative organism is shown in table 6.

TABLE 5

CAUSES OF SECONDARY PERITONITIS

1.	Acute appendicitis with perforation	79
2.	Perforation of the bowel associated with:	
	a. Meckel's diverticulum	13
	b. Volvulus	
	c. Ulceration of the bowel	
	d. Strangulation of the bowel	
	e. Necrosis and gangrene of the stomach	
	f. Duodenal ulcer	
	g. Trauma	
	h. Congenital malformations	
3.	Acute enteritis and intestinal intoxication	2
4.	Post-operative appendicectomy	2
5.	Post-operative gastrostomy	2
6.	Post-operative gastro-enterostomy	1
7.	Questionable	4

TABLE 6

CAUSATIVE ORGANISMS IN THE CASES OF SECONDARY PERITONITIS

B. coli	57
B. coli and enterococcus	3
B. coli and haem. strept.	2
B. coli and staphylococcus aureus	1
Enterococcus	1
Haem. strept.	3
B. pyocyaneus	2
Pneumococcus type XIV	1
TOTAL	70

The age incidence was on an average higher than the primary group, being 7·7 years, ranging from twenty months to thirteen years, with the sex being 65 per cent. males as compared with 35 per cent. females. The highest mortality rate was also confined to the infants under two years of age, with fifteen deaths out of sixteen cases, or a mortality rate of over 90 per cent.

The signs and symptoms as well as the diagnosis of appendiceal peritonitis are just as important to the paediatrician and general practitioner as they are to the surgeon, because if he diagnoses the case early and has it operated on immediately, the most important measure in therapy has been accomplished—that is, prevention. The early cases of peritonitis with a ruptured appendix gave a history of abdominal pain which usually was epigastric or umbilical in type but occasionally was localized in the right lower quadrant. The pains

were often vague and unreliable, especially in the younger age group, and were usually accompanied with or followed by vomiting. The results of the physical examination, which requires patience on the part of the examiner and ability to obtain the child's confidence, were difficult to assess, but palpation of the abdomen usually showed tenderness and occasionally spasm. The diagnosis of these cases was often not made until the peritoneal cavity was opened at operation. Unfortunately many of the cases included in this series were characterized by the anxious, hollow-eyed, shocked child who appeared similar to the younger child suffering from primary peritonitis. The average temperature on admission of this group was 101·3° F. and ranged between 98° and 105°. The white blood-count averaged 15,100 per c. mm. ranging between 4,000 and 30,000. The average number of polymorphonuclear granulocytes was 75 per cent.

The treatment of these cases consisted of the usually accepted measures which from time to time have been added to the treatment in order to bring down the high mortality rate. Practically all the children were put in Fowler's position depending on their age. The older children were put in high or semi-Fowler's, and the younger children, who do not maintain this position well, were put in low-Fowler's in a gatch-frame bed. Most of them received external heat to the abdomen, usually in the form of a light cradle but also by means of stupes or linseed poultices. Codeine and morphine were the sedatives of choice and were used in large enough doses to control pain, activity and nausea. The water balance was maintained in the majority of these cases by the continuous administration of two-thirds 5 per cent. glucose in distilled water with one-third normal saline in the infant group, a mixture which was found ideal for this purpose; and the older children received an adequate amount of intravenous 5 per cent. to 10 per cent. glucose in normal saline. In those patients in whom vomiting and distension was a disturbing element, a duodenal tube was passed and a continuous duodenal decompression set up as devised by Wangensten (1937). During the past year, under the direction of Dr. D. E. Robertson, this method has been supplemented successfully by the introduction of the Miller-Abbott tube for continuous decompression of the small bowel. All the requirements of Wright, Aaron, Regan and Milch (1939) in their management of sixty cases of diffuse peritonitis in adults and children with a mortality rate of 11·7 per cent., were fulfilled except the routine administration of blood, which they use to increase volume of the circulating blood, to attempt to restore the blood pressure in the shocked child and to supply blood to the peripheral tissues. Only eleven of the first cases received transfusions, mainly as an emergency measure.

In this hospital with several surgical services both the immediate surgical intervention and the conservative treatment have been tried. The literature contains favourable reports from both groups. Ladd (1938) and Elman (1938) are in favour of immediate operation as soon as the child's dehydration and shock have been successfully combated; while Coller and Potter (1934), and Adams and Bancroft (1938) follow a conservative method of therapy with modifications of the original Ochsner's treatment.

In this series fifty-one cases with peritonitis associated with perforated

appendix were operated on at the time of, or shortly after, admission. Forty-five of these cases were drained while six were closed. Twenty-eight cases received conservative treatment. In the operative group there were thirteen deaths, or a mortality rate of 25 per cent., whereas in the conservative group the mortality rate was 67 per cent. These figures may explain the gradually decreasing mortality rate of the past few years, the only difference in treatment being that more children were operated on early and fewer treated conservatively. In the past two years twenty-five cases were operated on early and only six treated by conservative measures.

A marked drop in mortality figures has been experienced since January, 1940, and although only twelve patients have been admitted with diffuse peritonitis they have all recovered in spite of age, method of operative procedure or seriousness of their general condition on admission. The only additions to the former therapy were the administration of the chemotherapeutic drugs, and in three cases a Miller-Abbott tube was passed because of marked distension. Among the twelve cases, ten received chemotherapeutic drugs, eight as a post-operative measure following early operation and two along with conservative treatment of the disease. Eight of the ten cases were given soludagenan intravenously from one to seven days until they were able to take the drug by mouth and then they were changed to sulphapyridine if their temperature and clinical findings had not entirely subsided. They remained on sulphapyridine from two to seven days. Five of these cases grew b. coli in the peritoneal fluid. One case received soludagenan for two days and was subsequently changed to sulphanilamide for six more days because haemolytic streptococcus as well as b. coli was cultured from the peritoneum. One of the conservatively treated cases received adequate doses of sulphanilamide and recovered.

In 1939 four cases received chemotherapy. Two were given sulphapyridine, one recovered, one died. The recovery was associated with a type XIV pneumococcus infection. The boy who died with a b. coli peritonitis was extremely ill post-operatively, and even though his blood reached a sulphapyridine concentration of 12·1 mgm. per cent. and he was kept continuously decompressed by the Miller-Abbott tube, he did not respond and died. The two other children were given sulphanilamide. The child who recovered had a haemolytic streptococcus in the peritoneal fluid and made an uneventful recovery post-operatively. The third child, who died, had a b. coli infection and did not respond to sulphanilamide because only one dose was given prior to his death eight hours after operation.

Conclusions

From the survey on appendiceal peritonitis it is felt that the mortality rate has been appreciably cut down by the use of the chemotherapeutic drugs just as it was in the cases of primary peritonitis. There is no question that the best method of treatment in these cases is to diagnose the acute appendicitis before rupture. However, in the practice of a children's hospital, neglected cases in which the parents have not called in a physician until after perforation, in which

the indiscriminate use of laxatives and cathartics has been made for the treatment of abdominal pain, and in which acute appendicitis has been missed, will continue to be admitted. Chemotherapy, although it will not take the place of any of the surgical measures previously mentioned, has proved to be another weapon in the armamentarium against appendiceal peritonitis as well as a specific for primary streptococcal and pneumococcal peritonitis.

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HELIUM-OXYGEN INHALATION

A RECENT ADVANCE IN THE TREATMENT OF LARYNGITIS AND TRACHEITIS

BY

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In 1934, Dr. Alvan Barach, of the Department of Medicine, Columbia University, New York, published the first paper on the therapeutic use of helium and oxygen mixtures. His work has created great interest because, as stated by DuBois, it marks the introduction of a new principle in therapeutics.

Helium is a non-combustible, odourless, monatomic inert gas with a molecular weight of 4 and therefore a specific gravity only one-seventh that of nitrogen and one-eighth that of oxygen. Its value in medicine depends entirely on its physical properties of low specific gravity and rapid rate of diffusion. A mixture of 79 per cent. helium and 21 per cent. oxygen is about one-third as heavy as air, and as 100 per cent. oxygen which is slightly heavier than air. Barach reasoned that the force required to move a column of gas to and from the lungs is proportional to the molecular weight of the gas, other things being constant. A vast amount of experimental work has been done on dogs and on human subjects. His results show that when helium-oxygen is used there is a decrease of 25 to 54 per cent. in inspiratory and expiratory pressure, a decrease in total pulmonary ventilation, and a comparable reduction in respiratory effort.

The biologic inertness of helium is proved by the fact that mice have lived three months in helium-oxygen atmospheres without apparent injury. Extensive studies of the effects of helium upon the human body have been carried out by the United States Navy with regard to its use in 'divers' disease.' No ill effects have been observed in patients.

The pathology of unrelieved respiratory obstruction in the large or small air passages is development of congestion and oedema in the lungs. Moore and Binger (1927) found that these changes take place in dogs subjected to inspiratory obstruction alone, but do not occur when the animals expire against obstruction. Barach and Kernan (1937) also find that pathological changes in the lungs are minimal during expiration against resistance, whereas severe pulmonary congestion and oedema at the hilar and basal regions of the lungs, with emphysema at the periphery, occur during inspiration against obstruction. They find that the great negative pressure induced in the chest during forced inspiration is the causative factor. The influence of the pathologically elevated intrapleural pressure, which Barach finds may be up to seven times the normal in dogs and in asthmatics, is primarily to exert suction on the pulmonary capillaries with exudation of serum, and later to cause congestion, oedema,

dilatation of the right heart and circulatory failure. When helium-oxygen is administered, particularly under slightly positive pressure, the negative intrapulmonary pressure is reduced one-quarter to one-half and exudation is stopped.

In clinical studies Barach finds that the use of helium-oxygen mixtures in obstructive conditions of the larynx, trachea and bronchi can compensate for a 50 per cent. obstruction in the lumen, and in some cases can obviate the need of tracheotomy. It also relieves dyspnoea in cases of obstruction below the level where tracheotomy would be helpful.

In one series, twenty-one cases have been studied at the Babies Hospital, New York. Specific diagnoses are not given, but all cases showed intercostal and substernal or suprasternal retraction. Of the twenty-one cases, five were excluded because they were moribund or helium had to be withdrawn prematurely. Sixteen cases remained for clinical judgment; of these three had a degree of obstruction too great for helium to relieve. In eight cases helium-oxygen was temporarily helpful for periods up to eight days, after which tracheotomy was done, either because the expected duration of obstruction made helium-oxygen therapy too expensive or because the obstruction progressed to an unrelievable degree. Of these eight cases, four lived and four died. In none of the cases was there any reason to believe that earlier tracheotomy would have helped, while the reverse is conceivably true. In every instance the patient was in better condition to withstand operative procedure. Five cases were relieved and recovered without tracheotomy.

Another series of twenty-one cases was published a year later by Barach and Kernan (1937). Case summaries are given.

Fifteen of these patients were in the paediatric age group and ten were under two years of age. Of the ten patients under two, six lived and four died. Of the six who recovered, three eventually required tracheotomy, for one of the reasons given above, but recovered uneventfully. A fourth patient was a year-old infant who had laryngotracheitis with cultures showing pneumococci, haemolytic staphylococci and haemolytic streptococci. This patient was discharged cured in five days. A fifth had a laryngitis with oedema which was treated for two days with helium-oxygen and was discharged cured on the sixth hospital day. The otolaryngologist felt that in this instance tracheotomy would have been inevitable without the aid of helium. Of the four deaths, two were due to broncho-pneumonia, six and three days after tracheotomy respectively. The third was a two-and-a-half months old premature infant who died of broncho-pneumonia, and the fourth infant died of haemolytic streptococcal sepsis and pneumonia. It is to be noted that both of these series were reported before the use of sulphanilamide, or sulphapyridine, became common. The authors feel that mortality might have been reduced further by the use of helium under slightly positive pressure.

In every instance, regardless of the final outcome, dyspnoea was markedly relieved and the general condition of the patient improved. The most favourable field is for inflammatory swelling of the air passages due to infection or mechanical irritation and instrumentation. The patient can frequently be tided over with helium and oxygen until the infection subsides without surgical intervention. The only quick relief for obstructive dyspnoea that compares in

efficiency with helium-oxygen is the passage of the bronchoscope as a preliminary to tracheotomy, and even this may result in sudden death.

To date, helium-oxygen inhalation has been used most extensively in the treatment of intractable asthma with results which are not obtainable by any other existing method of therapy. Patients apparently moribund in status asthmaticus, who were refractory to epinephrine, regained epinephrine-sensitivity in periods of helium-oxygen inhalation varying from one hour to five days. It is of proven value, experimentally and clinically, in emphysema, bronchiectasis and pulmonary fibrosis. Other conditions in which benefit has been reported are cardiac dyspnoea, post-operative atelectasis, unresolved pneumonia, laryngeal oedema following surgical procedures on the larynx and thyroid, and oedema following x-ray therapy. Its use in cases with marked respiratory depression and oncoming paralysis from high spinal anaesthesia suggests a possible use in poliomyelitis.

Details of the method of administration are given in Barach's original publication. The gas must be given in an absolutely air-tight system. Any small leak allows nitrogen to enter and nullify the effect. The ordinary oxygen tent is not helium-proof. The best apparatus for patients of all ages appears to be the Benedict helmet type of hood. For older children, oronasal masks may be used. Tanks with helium and oxygen pre-mixed are used, and extra oxygen may be added when needed from a separate tank. The danger of using tanks of pure helium is that the oxygen may be forgotten and asphyxiation occur suddenly. Because of the expense, the helium is usually rebreathed.

The inhalation may be given in periods of fifteen minutes to one hour or longer, repeated three to six times a day. Adults have inhaled helium-oxygen mixtures almost continuously for many hours without ill effect.

In conclusion, it has not been suggested that helium-oxygen inhalation replaces chemotherapy and surgical procedures in the treatment of laryngitis and tracheitis, but only that it be used as a valuable adjunct to the therapy of what has thus far proved a discouraging disease.

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NEPHROLITHIASIS IN CHILDREN

BY

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The following two cases are examples of nephrolithiasis in children recently observed in the Hospital for Sick Children, Toronto.

Case 1. J. C., a boy aged thirteen years, was previously in hospital in December, 1939, with two days' history of frequency and haematuria. The urine showed a cloud of albumin and was loaded with red blood cells. The non-protein nitrogen was 67 mgm. per cent., the creatinine 1·8 mgm. per cent. A diagnosis of acute haemorrhagic nephritis was made. His condition cleared up on the usual treatment and he was discharged in six weeks. He was followed in the out-patient department, and the urine remained clear for two months; he then had dysuria and passed two stones. He was readmitted April 1, 1940, for investigation. Analysis of the stones showed calcium oxalate and magnesium and calcium phosphate. X-ray showed many small bilateral calculi in the calices and bilateral hydronephrosis, especially the left side. The non-protein nitrogen, creatinine and cholesterol were normal, but the urine concentrated to a specific gravity of only 1010 (volume 70 c.c.). Urine culture gave no growth from bladder or ureters. Blood calcium on admission was 13·2 mgm. per cent., phosphorus 4·1 mgm. per cent. Subsequent estimations were normal and below normal. Phosphatase was 26 units. X-ray examination of the long bones was negative. Calcium balance was negative with two-thirds excreted in the urine.

Following an unsuccessful attempt to dissolve the stones by medical treatment, a left pyelolithotomy was done on May 30, 1940, to be followed by a similar operation on the right side at a later date.

Case 2. The second case was treated surgically. B. M., a girl, was aged two-and-a-half years when first admitted in October, 1937, with bilateral renal calculi. Kidney function tests were normal. The urine cultured bacillus coli. Right nephrolithotomy was performed and three calcium phosphate stones removed. She returned in November, 1937, with a right ureteral calculus as well as those in the left kidney pelvis. The urine concentrated to a specific gravity of 1015. B. coli were found in the urine on culture. In January, 1938, a left nephrolithotomy was done and three calcium carbonate stones removed. During that year she passed stones on three occasions and returned in December, 1938, with a stricture of the left ureter, which was dilated, and left pyelonephritis; new stones were present on the right side. She remained moderately well for three months and then returned in March, 1940, with severe pain in the left side and a soft fluctuant mass—an infected hydronephrosis. X-ray showed bilateral calculi. Non-protein nitrogen was 109 mgm. per cent. and creatinine 3·45 mgm. per cent. The haemoglobin was 43 per cent. Despite transfusion, fluids and irrigations by indwelling ureteral catheters, she died suddenly April 12, 1940, at five years of age. No autopsy was obtained.

At this hospital, since 1924, there have been four other recurrences of nephrolithiasis. Three of these followed one to two years after a nephrectomy for unilateral stone on the opposite side, and were removed by lithotomy without further trouble. The other was a boy (L. D.) aged twenty-three months on admission in June, 1924, with bilateral renal calculi and a left ureteral stone. These were removed from the left kidney and ureter and on analysis showed calcium carbonate and triple phosphates. Pyuria persisted and the child had an acute flare-up with anuria in December, 1925. X-ray showed a large calculus in the right kidney pelvis and multiple stones in the left, and a diseased and functionless left kidney. Following right nephrolithotomy and left nephrectomy, symptoms and pyuria entirely cleared.

There have been fifty-two cases of urinary calculi at the Hospital for Sick Children, Toronto, since 1924: three urethral, one vesical, sixteen ureteral, and thirty-two renal. In the latter group the average age at onset was seven years, with range from two months to thirteen years. Sex incidence was seventeen females to fifteen males. Seventeen were right-sided, three left-sided and seven bilateral. The commonest symptoms were pain, vomiting, haematuria, frequency and passage of stones. The urine showed white cells, red cells and albumin. Of fourteen recorded estimations of non-protein nitrogen, six were greater than 35 mgm. per cent. Urinary infection was present in thirteen cases; absent in ten ; not reported in nine. The coli group of organisms was the most frequent type, being present in eleven; staphylococcus aureus in one ; micrococcus ureae in one; streptococcus haemolyticus was present in two; and staphylococcus albus in one in association with the colon bacillus.

TREATMENT. In nine cases the stone was passed, with cure in six. Operations were performed as follows: nephrolithotomy in nine cases, nephrectomy in five, nephropexy in one. There was no operative mortality. One death was attributable to the lithiasis (B. M.); four deaths occurred from other infection, with stones found at post mortem, but with no symptoms (the other bilateral cases).

DIAGNOSIS. Seven cases had one to two previous admissions with symptoms referable to stone and diagnosis of: abdominal pain, two cases; acute nephritis, two cases; chronic appendicitis, two cases; intestinal obstruction, one case.

Etiology. Experimentally stones have been produced by artificial hyperexcretion of oxamide, calcium oxalate, calcium carbonate; by parathormone or large amounts of vitamin D, producing excessive calcium excretion in the urine; by impregnation of urinary epithelium with crystalline matter and infection, lime salts being precipitated; and by vitamin A starvation causing keratinization of urinary epithelium and lime salt precipitation in alkaline urine.

Clinically, phosphaturia, oxaluria, uraturia are associated with an increased incidence of calculi. Cystin, xanthin and fibrin stones are also found with hyperexcretion. Hyperparathyroidism produces excess calcium excretion in the urine and bilateral lithiasis. Decreased solubility and precipitation of

crystalloids may also be produced by abnormal colloid changes, even though the concentration is not increased.

Infection by urea-splitting bacteria plays a part by precipitating lime salts in the epithelium and by preventing acidification of the urine by the production of ammonia. In a series in Cleveland (Higgins and Mendenhall, 1939) this was present in 77 per cent. of cases. Also focal infection was found in 57 per cent. of cases, suggesting an association. Other observers give figures varying from 20 to 60 per cent.

Urostasis as a primary cause has no clinical or experimental proof but is important in relation to stagnation and infection. Urinary reaction is an important factor in maintaining solution and within certain limits determines the composition of the stone. Amorphous phosphate, carbonate and triple phosphate are precipitated in intensely alkaline urine. Urates, oxalates and crystalline phosphate and carbonate are precipitated in neutral or slightly acid urine—oxalates pH 5·9; urates 5·6; phosphates 6·2; uric acid 6·5. Experimentally alkaline stones will not form in acid urine, whereas alkalinization intensifies the process.

Malnutrition and vitamin A deficiency are suggestive factors, but proof is not clinically conclusive. Other factors are bone diseases, foreign bodies, bacterial clumps and sutures.

Medical treatment. Many methods have been tried in an attempt to dissolve urinary calculi. Small stones have been dissolved by continuous irrigation with phosphoric or other weak acids, by means of indwelling catheters, but denser stones, especially of oxalate and urate, have not responded to this treatment. Crowell used alkaline lavage in dealing with cystine stones.

Acid ash diet with vitamin A was popularized by Higgins (1939) and others. Soft calcium phosphate and carbonate stones not infrequently dissolve, but denser ones, with compaction and secondary internal crystallization are unaffected. The pH shift is often difficult to decide, as stones are usually mixed and certain types are found in both alkaline and acid urine. Keyser (1939) reports six alkaline calculi dissolved by acidification and two urate ones by alkalinization, but states that this method usually fails.

Phosphaturia can be corrected with sodium benzoate and glycocoll without change in urinary reaction. This is due to the production of hippuric acid, which increases the solubility of calcium phosphate. Rapidly recurring stones have been successfully prevented by this method.

Dissolution is therefore usually unsuccessful and should be attempted only with softer stones and for a short period (a few weeks), or where surgery is prohibited.

Surgical treatment. Nephrolithotomy is the method of choice, and the following precepts for the prevention of recurrence of calculi should be observed:

Be sure to remove all the stones; have them analysed. X-ray immediately and at regular intervals for several years. Correct any metabolic errors producing hyperexcretion, and investigate when hyperparathyroidism is suspected. Give a diet low in the stone-forming crystalloid and with acid or alkaline ash as indicated. To maintain alkalinization or acidification, drugs may be necessary

(e.g. urate stones, low purine diet and alkaline ash; oxalate stones, low oxalate diet, acid ash and vitamins B and D, associated with an endogenous source of oxalate; phosphate and carbonate stones, acid urine). The pH of the urine should be estimated with nitrazene paper by the patient. Give vitamin A. Eliminate infection by drugs such as sulphanilamide or mandelic acid. Remove foci of infection. Correct urostasis. Give at least two quarts of fluid daily.

Due to these measures, the incidence of recurrences of calculi has sharply decreased in the past few years, from about 30 to 50 per cent. in 1915 down to about 5·3 per cent. at the present.

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HODGKIN'S DISEASE IN CHILDREN

BY

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This disease was first described in 1832 by Hodgkin. It is a subacute or chronic illness characterized by painless and progressive enlargement of lymph nodes, involvement of other organs in a widespread pathological process, sometimes accompanied by fever, and resulting in anaemia, cachexia and finally death. The disease occurs more often in males than females in the ratio of two to one, and more often in adults than children. In a series of 173 cases in Baltimore only 2·5 per cent. were in children.

The etiology of the disease is still undecided, some believing it to be an infectious granuloma and others that it is a neoplasm. The coincidence of tuberculosis and Hodgkin's disease in the same patient has been confusing. Tubercle bacilli cannot be isolated from pure cases of Hodgkin's disease, and so far it has not been transmitted to lower animals.

Pathologically there is a hyperplasia of the lymphoid tissues everywhere, the superficial and deep nodes, and the lymphoid tissue of bones, organs and nervous system. Histologically there is proliferation of the reticulo-endothelial cells, eosinophils and lymphoid cells. Certain of the reticulo-endothelial cells assume the giant multinucleated form known as Dorothy Reed cells. In the later stages fibrosis may replace most of the cells. The glands on examination vary in consistency from soft to elastic or hard, depending on the stage of the disease. They are discrete and not attached to skin. A single group may be involved at the onset, but the involvement soon spreads.

Blood findings are not diagnostic. A progressive secondary anaemia is characteristic. Usually there is a normal total leucocyte count or a slight leucopenia. In more advanced cases the total white count is increased with a polymorph leucocytosis, a relative increase of monocytes and decrease in lymphocytes.

The first symptom is usually a painless swelling of one or more groups of superficial nodes. The areas most frequently involved are, in order, the cervical, supraclavicular, axillary and inguinal. A characteristic of Hodgkin's disease in its early stages is that unilateral lymph areas are attacked with greater frequency than symmetrical areas. In other forms of lymphoblastoma, such as lymphosarcoma and leukaemia, the involved nodes are more apt to be symmetrically enlarged.

Often an acute upper respiratory tract infection, a dental abscess, or one of the acute exanthemata of childhood precedes the onset. In some cases the

first glands involved are mediastinal or mesenteric, causing cough, dyspnoea, gastro-intestinal symptoms or a sense of heaviness in the abdomen due to an enlarged spleen. In others weakness, loss of weight, pallor, or unexplained fever, may be the first symptoms.

In a series of nine cases in children reported by Limper (1939), the initial symptoms were enlarged superficial glands in three; cough, with or without fever, in four; herpes zoster in one; and fever, pallor and haemorrhages in one. In the past ten years there have been thirteen cases of Hodgkin's disease admitted to this hospital. The initial symptoms were: fever in five cases; loss of strength in five cases; pallor in four cases; cough in two cases. Only three of the thirteen cases had the Pel-Ebstein type of fever. Limper reports only two of his nine cases in children having this symptom.

Splenomegaly and hepatomegaly are infrequent in early cases, but the spleen is enlarged in from 60 per cent. to 70 per cent. of advanced cases, and the liver in about 35 per cent. Both nodular and diffuse infiltration of bone marrow are common, and most frequently are seen in the vertebrae in children, and less often in the sternum and femur. The x-ray picture is that of osteolysis, resembling metastatic carcinoma. Cough and dyspnoea are the most frequent symptoms of mediastinal gland involvement, which does not occur without palpable cervical, supraclavicular, and axillary adenopathy. There is nothing pathognomonic in the x-ray picture of mediastinal Hodgkin's disease, which shows thickening of the hilar areas going on to a widening of the mediastinum, and invasion of adjacent lung fields. Pleural effusion is rare in children with mediastinal Hodgkin's disease.

Some type of cutaneous manifestation occurs in about 30 per cent. of cases, and includes simple pruritus, ulcerated papules similar to scabies, herpes zoster, and generalized exfoliative dermatitis. Pigmentation is frequently seen.

Of the thirteen cases admitted to the Hospital for Sick Children, Toronto, in the past ten years, eleven have been boys. The youngest was four years old and the oldest was twelve. The average age was eight years. The average duration of symptoms before death was nineteen months, the shortest period was three months, and the longest four and a half years. Eleven of these children had enlarged cervical glands, and one had enlarged axillary glands, on admission. Blood findings were not characteristic, but showed a varying degree of secondary anaemia, and decrease in lymphocytes.

The clinical course of Hodgkin's disease may be divided into three periods:

(1) The latent period, which is usually protracted, lasting from several months to several years, and usually causing no subjective symptoms. During this period involvement of cervical nodes occurs in 50 to 75 per cent. of cases, axillary, retroperitoneal, inguinal and mediastinal glands being involved less frequently. However, Ewing believes that though enlargement of cervical glands first attracts attention, primary enlargement of abdominal nodes, alone or combined with thoracic gland enlargement, occurs ten times more frequently than cervical primary enlargements, which are really extensions from an internal lesion.

(2) The period of progress and generalization. The feature of this period

lies in the appearance of pressure symptoms. In the neck, tracheal compression causes dyspnoea, which increases till the patient dies of strangulation; hoarseness or aphasia may result from pressure on the recurrent laryngeal nerve; pressure on the brachial plexus by masses above and behind the clavicle produces pain, trophic changes, and paraesthesia. In the axilla glandular enlargement may cause limitation of arm movement, and symptoms of pressure on nerves, veins and lymphatics. In the mediastinum, pressure on the trachea causes cough, dyspnoea, and the development of emphysema. Pleural transudates when they occur are usually serous and occasionally bloody. Direct pressure on the heart may cause cardiac embarrassment and displacement to the left. Jaundice may occur from compression of bile ducts by abdominal nodes. Oedema of the lower extremities may follow pressure on the vena cava. Cases with marked splenomegaly experience the characteristic heaviness and dragging sensation. Gastro-intestinal Hodgkin's disease is rare in children and usually simulates ulcerative colitis or may cause intestinal obstruction.

Fever is almost invariably present and often of the Pel-Ebstein type. Fever is not pronounced in the more chronic forms and some cases may run an entirely afebrile course. Weakness and prostration may be prominent, but more often the child is able to pursue his activities for months or even years. No dysfunction of the kidneys occurs except for an occasional mild albuminuria.

(3) As the disease progresses there is an exaggeration of the constitutional symptoms and the period of cachexia occurs with profound anaemia, hypotension, cardiac dilatation, and often anasarca. Those who are not strangled die of anaemia, or myocardial degeneration. Many die of intercurrent infections.

The **diagnosis** should be made as early as possible and should rest on biopsy, but the histological picture of hyperplastic tuberculous lymphadenitis, aleukaemic reticulosis, and retothelial sarcoma may be indistinguishable from Hodgkin's disease. The Gordon test, which was to have been a specific diagnostic test for Hodgkin's disease, has been found to depend solely on the presence of eosinophils in the material injected and has nothing to do with the disease itself. Eosinophils are present in 70 per cent. of glands of Hodgkin's disease, and it is in the same percentage of cases that the Gordon test is positive.

The most common complication in Hodgkin's disease is tuberculosis, which occurred in fourteen of 150 cases of Hodgkin's disease in one series. Emphysema, bronchiectasis, and pyogenic infections of lungs may complicate mediastinal involvement. Septicaemia, usually streptococcal, and endocarditis occur occasionally.

Treatment consists in irradiation of the enlarged glands, either with radium or with x-ray. Arsenic is useful, especially in relieving pruritus. Treatment of anaemia is indicated. Surgery is advisable in some cases for the relief of pressure symptoms. Malignant granulomatosis, by reason of the lymphoid character of its lesions, is exceptionally radio-sensitive. The effect of x-ray therapy on the granulomatous tissues is destructive, and is followed by fibrosis in excess of that usually observed in untreated cases. The aim of treatment is to obtain as long remissions as possible by methodical destruction of all foci, deep

and superficial. Simple daily irradiation, using the rotation plan, for about five weeks, until sufficient total dose has been given, is apparently the method of choice. The average duration of survival is prolonged, and may be doubled or tripled.

The **prognosis** in untreated cases is hopeless. In the acute cases treatment offers little. It is best in those cases with enlargement of superficial glands, and is not as good in those cases with involvement of mesenteric or mediastinal glands. Burnam, in 1926, reported a series of 173 cases, of which twenty-eight were regarded as cured after periods of one to ten years. Since then Holt (1933) reports that Burnam has some patients who have had no recurrence after as long as fifteen years.

The average duration in Corbeille's series of children (1928) was 22½ months. One lived 5½ years.

Summary

Hodgkin's disease occurs with comparative rarity in children. Diagnosis depends on biopsy, and the blood picture is not diagnostic. It has been possible to follow seven of the thirteen cases admitted to this hospital in the past ten years. Six of these are dead after an average of nineteen months from onset of symptoms. The seventh is still under treatment. Treatment consists in x-ray therapy, the aim being to obtain as long remissions as possible. Although cures have been reported by some authors, none has occurred in cases treated in the Hospital for Sick Children, Toronto, in the past ten years.

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ICTERUS GRAVIS NEONATORUM WITH ERYTHROBLASTOSIS

BY

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Erythroblastosis means a widespread extra-medullary haematopoiesis evident chiefly in liver and spleen, but seen also in kidneys, pancreas, suprarenals and various other organs. It can be recognized only by histological examination of the organs. The amount and extent of the erythropoietic foci are comparable to the picture observed in a twenty to twenty-four weeks old foetus. Erythroblastaemia means the presence in the peripheral circulation of a greater number of nucleated red blood cells than the physiological maximum for the age. In the majority of full-term normal new-born infants the nucleated red cells, consisting of erythroblasts, normoblasts and megaloblasts, vary between five and ten per 100 leucocytes or about 1000 per c.mm. of blood. In exceptional instances they may reach twenty-five to thirty-five per 100 leucocytes. In the case of premature infants these figures are somewhat higher. Disappearing rapidly, the nucleated red cells are usually absent from the blood by the second or third day, and are seldom seen after the fifth day of life. In erythroblastosis this process requires about three weeks. Though the continued presence of nucleated red cells is very suggestive that a condition of erythroblastosis exists, a diagnosis should not be made unless other distinctive signs are present also.

Clinical features. There are three closely-related symptom-complexes which are dependent on the same underlying pathological process of erythroblastosis. They are: (1) universal oedema of the foetus; (2) anaemia of the new-born; (3) icterus gravis neonatorum. This paper will consider only the symptom-complex due to the disturbance of the haematopoietic system in which icterus is the most striking presenting sign, namely icterus gravis neonatorum with erythroblastosis.

The criteria for the diagnosis of this condition, as outlined in 1932 by Blackfan, Diamond and Baty of Boston are: (1) familial incidence of early and severe jaundice, (2) anaemia, (3) abnormally large numbers of nucleated erythrocytes in the blood, (4) enlargement of the liver and spleen, and (5) haematopoiesis to an extraordinary degree in the extramedullary sites. Since the first and second child in a family are frequently unaffected, and because sporadic cases frequently occur, a positive family history should not be a necessary qualification. The syndrome of icterus gravis is characteristic. It is often familial, and there may be a history that other members of the family died of

severe icterus or were born dead with oedema of the new-born. The infant is either born jaundiced, in which case the amniotic fluid and vernix may be a deep yellow, or jaundice develops within the first twenty-four hours. This is in contradistinction to physiological icterus neonatorum, which makes its appearance on the second or third day of life. The occurrence of jaundice in the first twelve hours should always cause concern. The liver and spleen are invariably enlarged and petechial or purpuric areas frequently seen. Oedema is occasionally present. Anaemia, masked by an increasing jaundice, is a rapid development. In some instances the red count may drop by as much as a million cells and the haemoglobin by 50 per cent. in twenty-four hours. Haemolytic hypochromic anaemia is possibly as characteristic of erythroblastosis as is erythroblastaemia and allows early diagnosis to be made. Cases of icterus gravis with marked erythroblastaemia may show a rapid diminution or even disappearance of abnormal red cells from the peripheral blood. This applies to untreated as well as to transfused infants. The white blood-cell count is usually increased. Infants with icterus gravis are frequently difficult to resuscitate at birth, exhibit a peculiar somnolence, and may have mild or even severe convulsions. Coincident intracranial haemorrhage is a fairly common occurrence.

Various diagnoses were made on admission, including septicaemia, haemolytic anaemia, haemorrhagic disease of the new-born, intracranial haemorrhage, suprarenal haemorrhage, icterus neonatorum, haemolytic jaundice, congenital lues and congenital atresia of the bile-ducts.

The **etiological factors** concerned in this disease are a much debated question. The Boston group has stated that the disease is a disturbance of the metabolism of the haematopoietic system resulting in a failure of maturation of erythrocytes or in an overgrowth of immature forms. The view held by the English group is that the embryonic haematopoiesis is a symptom and not a cause of the disease; a response to an increased demand for red cells as a result of excessive haemolysis. Neither theory explains all the facts. The other signs of the disease complex, the anaemia, haemosiderosis, oedema and icterus may all be related to the dysfunction of erythrocyte production. The icterus is primarily of a haemolytic type, the result of the destruction of red blood-cells. The continuation of this process may so overburden the liver cells of the young organism that functional inefficiency may occur and a greater degree of icterus result.

The **prognosis** formerly has been considered very grave. However, many infants undoubtedly suffer from icterus gravis in a mild form and recover without treatment. Of the more seriously affected group, about half died, and of those surviving, about two-thirds exhibited at a later date sequelae referable to the central nervous system as a result of jaundice of the nuclear masses of the brain, or 'kernikterus'. This nuclear icterus is responsible for a certain proportion of deaths occurring before the fifth day and may manifest itself in respiratory paralysis, convulsions, drowsiness or head retraction. The four cardinal signs of the late syndrome of nuclear jaundice are: (1) choreo-athetosis; (2) extra-pyramidal spasticity; (3) opisthotonos; (4) mental deficiency.

The **pathological picture** shows the lesions to be limited to the striatopallidal portions of the brain, which during the acute phase of the disease are stained

with bile pigment and show evidence of cell destruction. The late lesions show evidence of this previous destruction of nerve elements, as demonstrated by loss of nerve cells, demyelination and glial proliferation.

The **pathogenesis** remains obscure. It is supposed that, following some injury, the nerve cells and myelin sheaths are subsequently stained with bile pigments carried to them by the blood in the same manner as any intravital dye will localize in zones of injury and will leave unstained tissues which are not damaged. The nature of the injurious factor is purely speculative at present, but a sub-clinical type of intrauterine infection has been mentioned. The infant may have clinical signs of ' kernikterus ' with no post-mortem evidence, and, conversely, stained basal nuclei have been reported at autopsy when there was no evidence during life that such a condition might exist.

Survey of cases

On the whole the literature is very discouraging as regards the frequency with which this dreaded complication of icterus gravis occurs, and would lead to the belief that neonatal death from this disease is a relatively fortunate occurrence. That this is far from being the case is well illustrated by a survey of our own cases over the past ten years. During the years 1930 to 1939 inclusive, thirty-seven infants who fulfil the criteria required for the diagnosis of icterus gravis neonatorum were admitted to this hospital. Of these twenty, or about 54 per cent., died while in hospital, either of the disease, some associated congenital anomaly, or intercurrent infection. Of the surviving seventeen, one died at eight months of broncho-pneumonia and one at two-and-a-half years of osteomyelitis. Both of these exhibited head retraction, spasticity and marked mental retardation, the so-called syndrome of nuclear jaundice. Of the remaining fifteen children, eleven, ranging in age from six-and-a-half months to five years, have been followed. All are well and are normal physically and mentally, except that three of the group show a greenish-grey discoloration of their teeth. Another of the group, last seen at two months of age in 1933, was apparently normal at that time.

From these figures it is seen that approximately 46 per cent. survived the disease icterus gravis, in addition to which it may be accepted that at least 65 per cent. of those who survive do not develop ' kernikterus '. It can also be assumed that this figure may be slightly higher when the remaining members of the group are located.

Previous to January, 1935, the only form of treatment was repeated blood transfusion. At this time calcium gluconate was added and the following year intra-muscular liver extract. In an effort to evaluate the various combinations of treatment, the cases are divided into five groups (table 1). From this it is seen that those infants who had the advantage of calcium and liver in addition to transfusion comprise the largest number of recoveries.

Treatment consists primarily in early and frequent blood transfusions. They do not appear to arrest the haemolysis, but rather to tide the infant over a period of severe anaemia until the haemolytic process ceases spontaneously. It

is our practice to transfuse as often as is necessary to maintain the haemoglobin above 60 per cent. Glucose may be given parenterally to protect the damaged liver cells.

TABLE I

RESULTS OF VARIOUS FORMS OF TREATMENT IN 37 CASES OF ICTERUS GRAVIS NEONATORUM, 1930–39

	NO TREATMENT; DIED SHORTLY AFTER ADMISSION	TRANSFUSIONS ONLY	TRANSFUSIONS AND LIVER	TRANSFUSIONS AND CALCIUM	TRANSFUSIONS, LIVER AND CALCIUM
Discharged from hospital, cured or improved.	0	4	2	1	10
Died	4	12	0	2	2

Because, theoretically, bilirubin is adsorbed by the calcium of the blood, it is the custom at the Hospital for Sick Children, Toronto, to increase the available calcium by the intravenous administration of 10 c.c. of a 10 per cent. solution of calcium gluconate at the time of the first two transfusions. It is hoped by this means to prevent the excess of bile pigment from staining the vital tissues, especially the nuclear masses of the brain. Liver extract in doses of 1 to 2 c.c. (20 to 40 grammes) daily, is given intramuscularly for ten to fourteen days. Its value is doubtful.

The hyperplastic anaemia stage lasts as a rule from two to three weeks and is followed by an aplastic or hypoplastic stage lasting from four to six weeks. During this latter period cerophyll, in doses of four to six teaspoons, added to the daily feeding has a definite therapeutic value.

Conclusions

1. Icterus gravis neonatorum with erythroblastosis is a definite clinical entity with characteristic syndrome, blood picture and pathology.

2. Although our series is small, it would seem that the incidence of basal nuclear jaundice as a late result of the disease has been over-estimated.

3. In evaluating the results of therapy, it would appear that a combination of repeated transfusions, intravenous calcium gluconate and intramuscular liver results in the greatest number of uncomplicated recoveries.

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THE DEVELOPMENT OF VITAMIN K AND ITS CLINICAL USES IN THE NEONATAL PERIOD

BY

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Within recent years the paediatrician has gained many synthetic therapeutic aids. These include sulphanilamide and allied compounds, various members of the vitamin B complex, the anti-convulsant dilantin, and in addition an anti-haemorrhagic agent which has been called vitamin K.

It is eleven years since Dam (1929, 1930), of the University of Copenhagen staff, attempted to determine if cholesterol could be produced in newly hatched chicks on a cholesterol-free diet from which the fats and allied compounds had been removed by ether extraction. He found that within a few weeks the chicks succumbed to severe haemorrhages from the skin and gastro-intestinal tract. To the absent anti-haemorrhagic factor he gave the name 'Koagulations-vitamin' or, as it came to be called, vitamin K. Dam further showed (1935) that this fat-soluble substance was widely distributed in nature, alfalfa, tomatoes and hog liver oil being effective in supplying the deficiency, alfalfa being the best source.

Although this anti-haemorrhagic factor in the normal diet of young chicks was postulated in 1929, it was not until seven years later that Schonheyder (1936), also of the University of Copenhagen staff, demonstrated a deficiency of prothrombin in the plasma of chicks on a vitamin K-free diet. The addition of vitamin K to their diet was followed not only by a rapid cure of their haemorrhagic tendency but also by a coincident rise of their plasma prothrombin to a normal value.

The clinical application of this research lies in those conditions in which there is a reduced amount of prothrombin in the circulating blood. A normal blood prothrombin is described by Butt, Snell, and Osterberg (1939a) as dependent on four factors: (1) there must be adequate amounts of vitamin K in the diet; (2) there must be adequate amounts of bile salts in the small bowel to render the vitamin K soluble; (3) there must be a normal intestinal absorptive surface, through which the dissolved vitamin K may be absorbed, and ensure that the vitamin K does enter the portal circulation or the intestinal lacteals; and (4) there must be a physiologically normal liver, to employ the vitamin K in the production of prothrombin.

On this basis, then, a haemorrhagic tendency occurring in cases of obstructive jaundice is due to lack of bile salts in the bowel, often coupled with a malfunctioning cirrhotic liver. In some cases of coeliac disease in children (Fanconi,

1938), and in idiopathic steatorrhoea or sprue in adults (Clark et al., 1939), a reduced prothrombin content has been found, and is believed to be due to failure of the intestinal mucosa to absorb fats and fat-soluble substances, including vitamin K. In farming communities it is common knowledge that the dehorning of cattle pasturing on sweet clover is often followed by prolonged and sometimes fatal haemorrhage from the dehorning site; cattle fed on partly spoiled sweet clover hay have a reduced prothrombin plasma content, presumably due to a mal-functioning liver damaged by toxins liberated by intestinal fermentation of this feed (Roderick, 1931).

The hypoprothrombinaemia of new-born infants is of greatest interest to paediatricians, as the basis of neonatal haemorrhagic disease. Several investigators (Quick and Grossman, 1939; Bray and Kelley, 1940) during the past twelve months have shown that following birth there is a physiological decrease in the prothrombin content of the blood, with a subsequent spontaneous restoration to normal values. This is complete by the fourth day of life when the decrease has been small, or by the sixth day when there has been marked reduction. It is in those cases in which prothrombin decrease has been greatest and prothrombin restoration takes longest that the severe spontaneous haemorrhages, recognized clinically as haemorrhagic disease of new-born, occur.

The cause of this deficiency is suggested by Quick and Grossman (1940) to be due to an inadequate storage of prothrombin or of vitamin K in the foetus. Presumably as soon as the baby is born the physiological demands promptly exhaust the available prothrombin, and since there is apparently neither a reserve of this substance nor of vitamin K a marked decrease of prothrombin occurs. Milk, a poor source of vitamin K, provides little help. The liver of the new-born infant is only able to secrete small amounts of bile (Marriott, 1935), so that the capacity of these infants to absorb fats is limited. Another factor is the hypermotility of the gastro-intestinal tract during the first week of life. The greatest source of vitamin K during the first few days of life would appear to be its synthesis by bacteria introduced into the intestinal tract following birth; considerable amounts of vitamin K have been shown (Almquist et al., 1938) to be present in pure cultures of staphylococcus aureus, bacillus coli, bacillus cereus, bacillus subtilis, and the tubercle bacillus, of which mention will be made later.

Numerous reports as to the efficacy of vitamin K preparations, producing a sharp reduction of the prothrombin time and simultaneous cessation of haemorrhage in cases of neonatal haemorrhagic disease, have been forthcoming during the past fourteen months, in March, 1939, from Waddell, Guerry, Bray, and Kelley of Virginia, and in December, 1939, from Dam, Tage-Hansen, and Plum, of Copenhagen. As an example, the Virginia workers reported the cases of two infants, both four days old; one had a greatly prolonged prothrombin time of 420 seconds, and the other one of 210 seconds. To both infants 2 c.c. of a concentrate rich in vitamin K were given by mouth, and in both instances there was reduction of their prothrombin times to almost normal values in two hours.

Such a report answers the criticism of the doubtful effectiveness of vitamin K, based on the self-limiting nature of haemorrhagic disease of the

new-born. Bray and Kelley (1940) showed that the return of the prothrombin level to normal in the natural course of events is a gradual process, extending over twenty-four to seventy-two hours, depending on the extent of the previous prothrombin fall, whereas, following vitamin K administration, the prothrombin restoration to normal is extremely rapid (Waddell et al., 1939; Snelling, 1940), over a period of two to four hours.

While interest in the possibilities of vitamin K was being aroused in various clinics, Almquist and Klose (1939a) announced that a synthetic substance, phthiocol, had definite curative effects on chicks on a vitamin K-free diet. Phthiocol was first isolated from cultures of tubercle bacilli (Anderson and Newman, 1933a), later synthesized, and shown (1933b) to belong to a group of organic compounds called naphthoquinones. The starting-point of the studies that linked up the naphthoquinones and natural vitamin K was work by Dam (1939) showing that certain naphthoquinones and natural vitamin K had identical ultra-violet absorption spectra.

A variety of naphthoquinones has been found to be effective in curing haemorrhagic disease in chicks (Ansbacher and Fernholz, 1939; Almquist and Klose, 1939b), but the most active and least toxic one has been shown to be 2-methyl-1,4-naphthoquinone, a single dose of 1 milligramme orally, intramuscularly or intravenously being sufficient to cure this disease effectively and rapidly. The honour of being the first to use the naphthoquinone, phthiocol, with clinical success goes to a group of Iowa City workers, Smith, Ziffren, Owen, and Hoffman (1939), who reported giving phthiocol intravenously to a case of obstructive jaundice with good results. This work has been confirmed subsequently by the same workers and also by Butt, Snell, and Osterberg (1939b).

The first report of the use of methyl naphthoquinone in neonatal haemorrhagic disease was by Nygaard (1939), who gave 5 milligrammes intramuscularly with 5 milligrammes by mouth, normal prothrombin values resulting in ten to twenty-four hours. Rhoads and Fliegelman (1940) reported the use of this drug given in 1-milligramme doses orally to new-born infants with haemorrhagic tendency, with similar results. More recently the intramuscular injection of $\frac{1}{3}$ to 1 milligramme of methyl naphthoquinone dissolved in corn oil was reported by Andrus and Lord (1940), with prompt response of prothrombin levels. The efficacy of this substance in actual neonatal haemorrhagic disease has been further demonstrated (Snelling, 1940) by work done at the Hospital for Sick Children, Toronto, during the past three and a half months.

In addition to the use of vitamin K preparations therapeutically, the use of vitamin K prophylactically should prove of increasing importance in the hands of paediatricians. In its prenatal use it has been reported by Hellmann and Shettles (1939) that the daily administration of 3100 Ansbacher units to two mothers for sixteen and thirty days before delivery not only doubled the maternal blood prothrombin content at delivery but tripled the prothrombin content of the infants' umbilical cord blood. Moreover, these same workers showed that about fifty per cent. of infants born prematurely had blood prothrombin levels so low as to be within the range reported for haemorrhagic disease. It is only necessary to recall the considerable incidence of fatal

cerebral haemorrhage in premature infants to realize the prophylactic potentialities of this anti-haemorrhagic agent when given prenatally.

In the neonatal period vitamin K therapy should be of real value. The frequent appearance of symptoms of intracranial haemorrhage on or about the third day of life, when correlated with the period of greatest reduction of prothrombin values, is disturbing. A suggested explanation (Grossman, 1940) is that minor injuries to intracranial blood vessels during delivery permit slow oozing to continue, owing to the faulty blood clotting mechanism, and since this mechanism becomes increasingly inefficient during the first three days of life, it is on or about the end of that time that the dread and often fulminating symptoms of intracranial haemorrhage appear. Waddell and Guerry (1939) therefore suggest a real indication for the oral administration of vitamin K, advising that 1 c.c. of a vitamin K concentrate be given at the end of the first twenty-four hours of life, $\frac{1}{2}$ c.c. at the end of the first forty-eight hours, and a second $\frac{1}{2}$ c.c. at the end of the first seventy-two hours, especially to prematurely born infants.

A further indication for its prophylactic use is preoperatively, when any surgical intervention is found necessary during the first week of life, so that any undue bleeding due to a low prothrombin level may be avoided.

In conclusion, it may be hoped that, by means of this new drug, methyl naphthoquinone, it will become possible not only to cure neonatal haemorrhagic disease but to place this disease in the group of preventable disease along with rickets, scurvy, diphtheria, and tetanus.

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CASE REPORT

GARGOYLISM

REPORT OF FOUR CASES

BY

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The first published description of the syndrome now known as gargoylism appears to be that given by Hunter (1917), although the late Dr. John Thomson, of Edinburgh, had in his clinical teaching recognized the condition as a disease entity as early as 1908 (Henderson, 1940). Some authors have adopted the eponym ' Hurler's syndrome,' though this is a misnomer, since Hurler's (1920) paper did not appear until two years after Hunter's. The literature relating to the condition has recently been extensively reviewed in this journal by Henderson (1940). The following reports add four new cases, and serve further to emphasize the familial nature of the syndrome.

Clinical records

Case 1. M.B. (fig. 1), female, aged four-and-a-half years, a sister of case 2, was admitted to hospital in October, 1933.

FAMILY HISTORY. The child is of French-Polish extraction. The other

FIG. 1.—Showing the two sisters D. B., aged three-and-a-half years, and M. B., four-and-a-half years.

siblings, with the exception of case 2, were normal, and the parents cannot remember any children like these amongst their immediate or distant relatives.

PRESENT ILLNESS. The child seemed normal until four or five months of age. At that time her mother noticed that her head seemed large and that she was continually perspiring. Her breathing became difficult and she developed a purulent nasal discharge. At times her respirations were difficult and were associated with a crowing sound. Her abdomen at this time was large and the navel protruded. A doctor was consulted, who stated that the infant was getting rickets and prescribed cod-liver oil, orange juice and thyroid tablets for a month. No improvement was noted during this time and the medicine was discontinued. The child's development was slow. She did not sit up until eleven months of age, did not stand until two years of age and was unable to speak at four-and-a-half years of age. Her first tooth appeared at twelve months.

PHYSICAL EXAMINATION. The general appearance is that of an underdeveloped, well-nourished, female child with coarse features, a large head, protuberant abdomen and obvious mental retardation. The head is symmetrically enlarged and the suture lines are palpable as grooves. There is a bulging area on the skull posterior to the ear on either side. The nose is broad, with a depressed bridge, and the lips are thick. The hair is thick and coarse and the eyebrows are thick and bushy. The eyes are widely spaced and protrude slightly; both corneae are uniformly cloudy. The pupils are equal, react to light, and there is no strabismus. The teeth are small and the incisors are separated. There is a profuse post-nasal discharge. The chest is symmetrical, with a rachitic rosary palpable. The lungs and heart are normal. The abdomen is large and the navel is protruding. The liver is palpable four fingerbreadths below the costal margin in the right mammary line. The spleen is palpable two fingerbreadths below the costal margin. There is a moderate kyphosis over the lower dorsal and upper lumbar spine; no scoliosis is present. The scapulae are fixed. The forearm and fingers are thickened and there is some limitation of extension at the elbow, wrist and finger joints. The knees appear large and also show limitation of movement. The reflexes are normal.

MEASUREMENTS	PATIENT	NORMALS (ENGLEBACH, 1932)
	INCHES	INCHES
Length ..	37	39·5 to 42·3
Head ..	20½	19·9
Chest ..	20½	21·0
Abdomen ..	22	19·7

RADIOGRAPHIC EXAMINATION shows abnormal thickness of the long bones (fig. 2), with rachitic irregularities in the diaphyses. The second, third and fourth metacarpals show pointed proximal extremities, and the wrists show three carpal ossification centres at four-and-a-half years of age. The skull is irregular in thickness, heavy over the occiput and thin over the temporal and parietal areas. The general structure is turricephalic in type and is associated with a bulging of the temporal and parietal bones. The sella turcica appears to be slightly enlarged.

LABORATORY EXAMINATION. Red blood-cells 4,500,000 per c.mm.; white blood-cells 9,000 per c.mm.; Polys., 68 per cent.; Lymphs., 32 per cent.; Haemoglobin, 85 per cent.

Blood cholesterol, 229 mgm. and 221 mgm.

FIG. 2.—M. B., showing rachitic changes in the long bones, the pointed metacarpals and three carpal centres of ossification.

Blood calcium, 9·4 mgm. ; Blood phosphorus, 4·0 mgm.; Blood Wassermann, negative.

Von Pirquet tuberculin test, negative.

PSYCHOMETRIC EXAMINATION by Kuhlmann's test. Mental age one to two years, I.Q. 26.

Case 2. D. B. (see fig. 1), female, aged three-and-a-half years, a sister of case 1, was also admitted to hospital in October, 1933.

PRESENT ILLNESS. This child seemed normal until six months of age, at which time her mother noticed that she was not as active as other children of her age. At eight months of age she began to breathe through her mouth because of a purulent nasal infection, and at times her respirations were of a crowing type. She was seen at that time by a physician and was given cod-liver oil for one month with no appreciable improvement. The child's development was slow. She could not stand until two years of age and could not walk or talk until three-and-a-half years of age. She was seen by a physician three months before admission and given thyroid tablets, which produced no demonstrable change.

PHYSICAL EXAMINATION. On examination she presents findings which are similar to those in case 1. She is an under-developed, well-nourished, female child of rachitic appearance who is mentally deficient. The skin is dry and somewhat thickened. The head is large and symmetrical but shows an area of bulging above and posterior to each ear in the region of the parietal and temporal bones. Frontal bossing is also seen. The eyes appear widely separated, protrude slightly, and the corneae are uniformly cloudy. The

pupils react to light, and there is no strabismus. Vision appears good. The nose is wide and shows flattening of the bridge. The neck is short and thick. The lips are thick, the teeth small and the incisors separated. There is a profuse post-nasal discharge. The chest is symmetrical, but shows rachitic beading at the costochondral junctions. A faint systolic murmur is heard in the pulmonary area. The abdomen is large and there is an umbilical hernia. The liver is palpable four finger-breadths below the costal margin, and the tip of the spleen is also palpable. The scapulae are fixed and there is limitation of extension of the extremities. The bones of the extremities appear shortened and thickened on palpation. There is marked kyphosis of the lower dorsal and upper lumbar spine but no scoliosis. Reflexes are normal.

MEASUREMENTS	PATIENT	NORMALS (ENGLEBACH, 1932)
	INCHES	INCHES
Length ..	34½	36·9 to 39·5
Head ..	20	19·6
Chest ..	20½	20·4
Abdomen ..	21	19·3

RADIOGRAPHIC EXAMINATION shows irregular, almost ovoid, vertebral bodies, with a shelf-like projection on their anterior margins (fig. 3). The long bones are uniform in density and are thicker than normal. At the wrists, two carpal ossification centres are to be seen at three-and-a-half years of age. The skull is somewhat irregular in thickness, being unduly heavy in the occipital region (fig. 4). The bones of the temporal and parietal regions are thin and bulge prominently. The sella turcica appears to be normal in size.

FIG. 3.—D. B., showing the ovoid shape of some of the vertebra with the anterior projections of the bodies.

FIG. 4.—D. B., showing the marked bulging of the temporal and parietal areas of the skull.

LABORATORY EXAMINATION. Red blood-cells, 4,500,000 per c.mm.; White blood-cells, 1,500 per c.mm.; Polys., 74 per cent.; Lymphos., 26 per cent.; Haemoglobin, 90 per cent.

Blood cholesterol, 235 mgm. and 260 mgm.; Blood calcium, 9·2 mgm.; Blood phosphorus, 3·0 mgm.

Blood Wassermann, negative.

Von Pirquet tuberculin test, negative.

PSYCHOMETRIC EXAMINATION by Kuhlmann's test. Mental age 9 mos. I.Q. 22.

Attempts were made at different times to trace these children, but without success. Just recently, however, it was learned that both had died from pneumonia within a year after discharge from hospital.

Case 3. E. A., male, (fig. 5 and 6) aged nine years, a brother of case 4, was admitted to hospital in November, 1939.

FAMILY HISTORY. These two children are of English extraction. Their parents and the other siblings are normal. There is no history of similar children in the immediate or remote relatives.

PRESENT ILLNESS. This child appeared to be normal until two years of age, at which time the family noticed that his development was slow when compared

FIG. 5.—Showing E. A., aged nine years.

FIG. 6.—Showing a close-up of E. A., aged nine years.

with that of the average child. He was examined by the family physician, and thyroid tablets were prescribed and were administered at sporadic intervals for four years. There was, however, no improvement with this medication. In 1935 the boy had a severe attack of measles and later in the year a hernial repair. In 1939 the right patella began to slip laterally, and this orthopaedic deformity increased in severity until he was unable to walk. The early developmental history of this boy seemed normal. He had two teeth at seven months of age. He walked at one-and-a-half years, he said a few words and fed himself at two years. Some deterioration, however, gradually appeared and at three years of age he became unable to talk or feed himself. At the present time he is almost bed-ridden, incontinent and speechless.

PHYSICAL EXAMINATION. On examination he shows some degree of dwarfism, which particularly involves the extremities. He has a large head, coarse, ugly features, dry, coarse hair and coarse, shaggy eyebrows. The skin is dry and thickened; there are no pigmented areas. The secondary sexual characters are not present. The eyes are rather widely separated, and the nose is broad,

with a depressed bridge. The lips are thick and the incisor teeth are separated ; the other teeth are carious. On ophthalmoscopic examination the optic discs are pale, showing nerve fibres, and there are no corneal opacities. The neck is short and thick, the thyroid is not palpable. The chest is broad and symmetrical and the lungs and heart are normal. The abdomen is protuberant, and scars of bilateral herniotomies are present in the inguinal region. The umbilicus is herniated. The lower border of the liver is four finger-breadths below the costal margin in the mammary line. The spleen is not palpable. The extremities are short in proportion to the trunk and the hands are small and spade-like. There is limitation of extension of the elbows and knees and limitation of movement at the shoulders. On flexing the right knee the patella is seen to be displaced laterally and overlies the lower part of the condyle of the femur. On extending the limb it is returned to the mid-position. The reflexes are present and there are no cranial nerve lesions.

MEASUREMENTS	PATIENT	NORMALS (ENGLEBACH, 1932)
Length of body	47¼ inches	49·5 to 52·9 inches
Circumference of head ..	22 ,,	20·9 inches
Circumference of chest ..	25 ,,	24·6 ,,
Circumference of abdomen	22 ,,	22·3 ,,
Span	44½ ,,	49·1 to 52·9 inches
Upper longitudinal measure	24½ ,,	24·7 to 27·1 ,,
Lower longitudinal measure	22¾ ,,	23·8 to 26·3 ,,
Weight	54 lb.	51·6 to 64·4 lb.

RADIOGRAPHIC EXAMINATION of the vertebrae (fig. 7) shows ovoid bodies, with a shelf-like projection of the anterior margins. The long bones (fig. 8)

FIG. 7.—E. A., showing the ovoid shape of some of the vertebra with the anterior projections of the bodies.

FIG. 8.—E. A., showing the rachitic changes in the long bones and seven carpal centres.

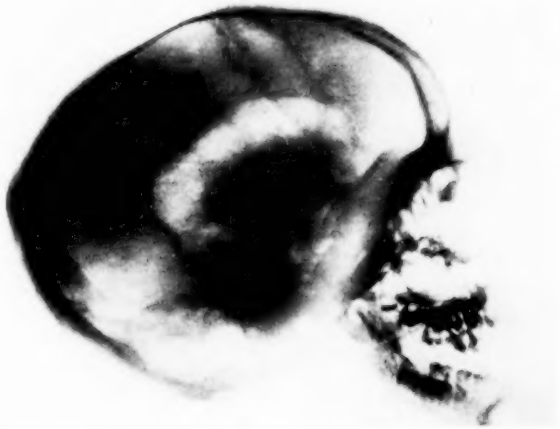

FIG. 9.—E. A., showing the dilatation of the lateral ventricles as demonstrated by an encephalogram.

show normal structure, and the wrists have seven carpal centres at nine years of age. The skull shows a slightly enlarged sella turcica with well-defined clinoid processes. An encephalogram (fig. 9) shows bilateral dilatation of both lateral ventricles with some slight cortical atrophy.

LABORATORY EXAMINATIONS. Red blood-cells, 5,300,000 per c.mm.; Haemoglobin, 85 per cent.; White blood-cells, 6,200 per c.mm.; Polys., 80 per cent.; Lymphos., 20 per cent.

Blood calcium, 9·7 mgm. per cent.; Blood phosphorus, 4·1 mgm. per cent.; Cholesterol, 150 mgm.; Phosphatase, 22 units.

PSYCHOMETRIC EXAMINATION by Kuhlmann's Pre-school Test indicated a mental development of $6\frac{1}{2}$ mos. and I.Q. below 10.

Case 4. F. A., male (fig. 10 and 11), aged nine years, a brother of case 3, was admitted to hospital in January, 1935.

PRESENT ILLNESS. During the first two weeks of life this child had many slight convulsions. At two weeks of age the thymus was irradiated and the convulsions then ceased. The early development of this child appeared to be

FIG. 10.—Showing F. A., nine years.

FIG. 11.—Showing a close-up of F. A., aged nine years.

normal. The first tooth appeared between seven and eight months of age. He sat alone at twelve to fourteen months, said single words at fourteen months, but could not say short sentences until he was over two-and-a-half years of age. He was seen by a physician at that time and a diagnosis of cretinism made. Thyroid was given irregularly for over two years and was accompanied by a short course of pituitary injections. There was, however, no improvement on this treatment. At four years of age the child began to lose the power of speech and the parents thought that he also became hard of hearing. At five years of age he had an attack of bronchopneumonia, and following this his teeth became extremely carious. At the present time the child is drowsy and sleeps a great deal of the time. When roused he is uneasy, restless and difficult to manage. Control of the bladder and bowel are now lacking and he is frequently incontinent. His appetite is variable, at times poor and at others ravenous. His gait is unsteady and he is unable to walk without support.

PHYSICAL EXAMINATION. This boy appeared short for his age and of low mentality. He did not respond to sounds, muttered unintelligibly and violently

resented examination. He had coarse, dry, red hair and the eyebrows were thick. The skin was thick; moderate hirsutism was present over the body and there was slight growth of pubic hair. His head was large and asymmetrical, with some flattening of the right forehead and a prominent bulging over the left ear involving the temporal and parietal bones. A similar prominence occurred on the right side, but to a lesser degree. The orbital ridges were prominent. The eyes did not react to light and accommodation. No corneal opacities were present. The nose was flat and wide, with prominent external nares. The lips were thick and everted. The teeth were markedly carious and the incisors were separated. The lower jaw was more prominent than normal. Respiratory and cardiovascular systems showed no abnormalities. The abdomen was not enlarged and no herniae were present. The liver margin was three finger-breadths below the costal margin in the mammary line but the spleen was not palpable. There was some limitation of movement of the scapulae and also of the knee and elbow joints. The reflexes were normal and there were no lesions of the cranial nerves.

MEASUREMENTS	PATIENT	NORMALS (ENGLEBACH, 1932)
	INCHES	INCHES
Length of body	47	49·5 to 52·9
Circumference of head ..	22	20·9
Circumference of chest ..	25	24·6
Circumference of abdomen	21½	22·3

RADIOGRAPHIC EXAMINATION showed thickened long bones of uniform density. The wrists showed seven carpal centres at nine years of age. The skull showed thinning of the parietal and temporal areas, with slight external bulging. The sella turcica was slightly enlarged. Encephalogram (fig. 12) showed dilatation of both lateral ventricles and poor cortical markings.

FIG. 12.—F. A., showing the dilatation of the lateral ventricles as demonstrated by an encephalogram.

LABORATORY EXAMINATIONS. Red blood-cells, 5,300,000 per c.mm.; White blood-cells, 9,100 per c.mm.; Polys., 74 per cent.; Lymphos., 26 per cent.; Haemoglobin, 88 per cent.

Blood Wassermann, negative; spinal fluid Wassermann, negative.

Von Pirquet tuberculin test, negative.

A formal psychometric test was not done, but the child was grossly retarded and would be classed as an idiot.

This boy was discharged from hospital without further treatment but died at home within four months.

Comment

One feature of these cases which has not been described as yet is the prominence of the skull above and posterior to the ears. On radiographic examination the parietal and temporal bones in this area appear to be quite thin, and this, with the associated prominence, results in a characteristic radiological appearance. This abnormality was particularly noted in cases 1 and 2, and to a lesser degree in case 4.

Conclusion

Four cases of gargoylism have been reported in this article. The first two cases (sisters) conform in all details to the classical description and are considered as complete forms of the syndrome. The latter two (brothers) did not show corneal opacities but conformed in all other respects and are considered as incomplete forms of the syndrome. No direct evidence was obtained to support the belief that gargoylism is due to a disturbance of lipoid metabolism, since none of these cases came to autopsy.

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THE CHANGES IN THE BLOOD PRODUCED BY DEHYDRATION IN INFANCY *

BY

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It is the purpose of this and a subsequent paper to record the result of a study of the effects of dehydration and the treatment of that condition carried out in a series of fifty-one infants in the years 1937–1938 during the tenure of a Caroline Harold Fellowship of the University of Birmingham. The objects of the investigation were : To determine the indications for the administration of fluid parenterally ; the best form of fluid to use ; the route by which it should be given ; the value of haematological and biochemical examination in forming a decision as to the most suitable fluid to use. In this paper the changes in the blood produced by dehydration are chiefly considered, and the subsequent paper is devoted to the treatment of that condition.

The majority of the children in this series were suffering from gastro-enteritis, but some were investigated before and after operation—chiefly for pyloric stenosis in infants and for hare lip and cleft palate in older children—and others who, on account of haemorrhage or for other reasons, were given blood transfusions. The investigations carried out on the blood comprised red cell counts, haemoglobin estimations, haematocrit readings and the estimation of plasma chloride and plasma protein concentrations. For these purposes very small amounts of heparinized blood (less than one-third of a cubic centimetre) were collected from the subject's heel or ear in tubes especially designed for the purpose ; it was thereby possible to carry out daily examination of the blood over long periods without causing an appreciable loss of blood to the patient.

Methods

Haematological. Red cells were counted in a Hawkesley's ' Improved Neubauer ' chamber, and strict precautions were adopted to ensure that all counts were comparable. Haemoglobin was estimated by Haldane's colorimetric method ; if the solution was cloudy a drop of liquor ammonii fortis was added to disperse the turbidity. It was found that this addition did not affect the ultimate reading of the haemoglobin, but, as an additional precaution, if ammonia had been added it was used in every subsequent haemoglobin determination in that case. Haematocrit readings were calculated by centrifuging

* Part of a thesis submitted for the degree of M.D. of the University of Cambridge.

specimens of heparinized whole blood at 8000 revolutions per second for half an hour, using specially designed micro-tubes made by Messrs. Baird and Tatlock. The results were recorded as percentages.

Biochemical. The blood was centrifuged within half an hour of collection and the plasma removed. If for any reason it was impossible to proceed immediately with the chemical investigations the plasma was placed in an ice-chest until this was possible. The changes in chloride and protein values after this treatment were always within the limits of experimental error. Chloride was estimated on 0·02 c.c. of plasma by Claudius's ultra-micro application of the open Carius method (Peters and van Slyke, 1931). Chloride values were calculated in terms of mgm. of NaCl per 100 c.c. of plasma, and in all references obtained from the literature the values are expressed in this way. Reasonable precautions were taken during the collection of specimens, but they were not taken under oil ; instead, it was decided that a standard method of collection was more practical. Provided that the plasma was removed at the earliest opportunity, and that the specimens were taken without undue shaking or exposure to air, the results were constant within 2 per cent. In a series of normal infants, however, since the specimens were collected at some distance from the laboratory, there was a greater interval between the collection of the blood and the estimation of chloride ; even so, the maximum range of the series was from 530 to 654 mgm. per cent. of NaCl (average 607), and only 19 (12 per cent.) of the 160 cases examined lay outside the usually accepted limits of 560 to 640 mgm. per cent. NaCl. This suggests that the procedure gives a reasonably accurate picture of the chloride content of the blood, and can be used to follow its variations from day to day.

In order to reduce the volume of blood required, and to simplify the procedure, a measure of the daily variation of the plasma protein concentration was obtained by estimating the total nitrogen, and multiplying the figure by 6·25, the result being the amount of plasma protein in grammes per 100 c.c. No correction was made for non-protein nitrogen, although it was realized that this would often be greater than normal. For this estimation 0·02 c.c. of plasma was diluted up to 10 c.c. and 5 c.c. and this diluted fluid was used for the determination, employing Folin's modification of the Kjeldhal method, followed by direct Nesslerization with Koch and McMeekin's Nessler solution.

The chloride in urine and food was estimated by the open Carius method as applied by van Slyke and Sendroy (van Slyke, 1923) and Eisenman (1929).

In the tables that follow certain abbreviations have been used :

Hbn.	Haemoglobin.
B.T.	Blood transfusion.
D. and V.	Diarrhoea and vomiting.
G-E.	Gastro-enteritis.
P.S.	Pyloric stenosis.
Imp.	Improved.
P.U.	Passed urine.
N.S.	Normal saline.
5 per cent. g-s.	5 per cent. glucose solution in normal saline.
5 per cent. g-½s.	5 per cent. glucose solution in half normal saline (0·45 per cent.).
10 per cent. G.	10 per cent. aqueous solution of glucose.
m.e./litre.	milli-equivalents per litre.

Ages are expressed as fractions of a year, e.g., 5/12 represents an age of 5 months.

CHARACTERISTICS OF DEHYDRATION

Dehydration may be defined as the condition in which the water content of the body tissues is diminished, using the term ' body tissues ' in its widest sense to include the skin, subcutaneous tissues, muscles, viscera and blood. It may result from deficient intake of water, excessive loss of fluid and salts, or a combination of these factors. The characteristic features of the condition may be considered under three headings, clinical, haematological and chemical. The chemical changes occurring in the blood of dehydrated children with gastro-enteritis and those with pyloric stenosis are not really comparable, since in gastro-enteritis the loss of fluid and base in the stools usually causes acidosis, whereas in pyloric stenosis the loss of chloride in the vomit may result in alkalosis. Consequently the chemical findings in the two conditions will be considered separately.

Clinical features

The infant's face, especially under the eyes, has a sunken and pinched appearance and the normal pigmentation under the lower lids is increased. The skin is dry and inelastic and tissue turgor is diminished, particularly in the subcutaneous tissues and muscles of the anterior abdominal wall. If the anterior fontanelle is still patent it is depressed, and the tongue and visible mucous membranes are dry. The pulse rate and respiration rates are increased ; there is a varying degree of pyrexia, oliguria, thirst and loss of weight. In the most marked type of dehydration, usually seen only in very severe gastro-enteritis, there may also be a peculiar ashen-grey colour of the skin, coldness and cyanosis of the extremities, a subnormal temperature and a restlessness which later gives way to drowsiness, stupor, or even coma. In such cases weakness is pronounced, and there may in consequence be difficulty in feeding and swallowing. Anuria may develop.

Haematological features

The viscosity of the blood is increased, and there is a diminished tendency to bleed from cut surfaces. The blood is more concentrated than normal and shows an increased red cell count, haemoglobin concentration and haematocrit readings. These features were demonstrated in the examination of forty-nine infants with varying degrees of dehydration. Of these, thirty-five suffered from gastro-enteritis and fourteen from congenital hypertrophic pyloric stenosis. The results obtained in the investigation of these patients are set out in tables 1, 2, 3. In table 1 are shown the results of examination of the blood carried out in thirty-one patients before parenteral administration of fluid, and table 2 summarizes the findings in the remaining eighteen cases, which, because of the seriousness of their condition, had all been treated with parenteral fluid before investigation of the blood. Many infants become more dehydrated during the course of their illness, and table 3 shows the most extreme changes which occurred in such children.

TABLE 1
THE CHANGES IN THE BLOOD IN DEHYDRATION

CASE	AGE	CLINICAL CONDITION	RED CELLS (MILLIONS PER C.MM.)	HAEMOGLOBIN (PER CENT.)	HAEMATOCRIT
15	3/52	Pyloric stenosis	6·62	128	66·2
27	8/12	Gastro-enteritis	4·44 5·54	80 92	35·9 41·6
28	6/52	Gastro-enteritis	4·28	96	42·0
34	3/12	Gastro-enteritis	5·30	92	43·2
42	3/12	Gastro-enteritis	4·58	82	35·2
57	8/52	Pyloric stenosis	5·35	98	—
58	5/12	Gastro-enteritis	6·33	86	44·4
59	5/12	Gastro-enteritis	6·55	94	—
63	5/52	Pyloric stenosis	5·93	102	50·0
66	8/12	Gastro-enteritis	5·36	80	38·2
67	9/12	Gastro-enteritis	7·00	88	43·6
68	2/12	Gastro-enteritis	4·60	86	39·3
69	9/12	Gastro-enteritis	5·74	86	40·1
70	4/12	Gastro-enteritis	5·00	82	40·0
72	2/12	Gastro-enteritis	5·43	93	44·9
73	3/12	Gastro-enteritis	5·65	104	45·6
74	7/52	Pyloric stenosis	6·24	105	46·6
75	6/12	Gastro-enteritis	6·31	90	—
76	10/52	Gastro-enteritis	4·31	78	—
78	7/12	Gastro-enteritis	7·17	100	—
83	4/52	Pyloric stenosis	5·86	114	—
88	5/52	Pyloric stenosis	6·33	124	—
89	3/12	Pyloric stenosis	5·62	98	—
90	6/52	Gastro-enteritis	4·57	92	—
94	4/52	Pyloric stenosis	7·01	128	58·7
98	6/12	Gastro-enteritis	6·49	88	42·7
100	9/12	Gastro-enteritis	7·20	100	52·2
102	6/52	Pyloric stenosis	6·06	122	52·2
103	5/52	Pyloric stenosis	5·62	103	45·6
105	5/12	Gastro-enteritis	6·40	83	39·4
Average			5·84	97	44·9

TABLE 2
THE CHANGES IN THE BLOOD IN DEHYDRATION

CASE	AGE	CLINICAL CONDITION	RED CELLS (MILLIONS PER C.MM.)	HAEMOGLOBIN (PER CENT.)	HAEMATOCRIT
2	8/12	Gastro-enteritis	6·00	92	46·7
4	5/52	Gastro-enteritis	6·01	114	44·4
14	6/12	Gastro-enteritis	5·63	78	38·9
17	3/12	Gastro-enteritis	6·59	108	51·7
33	6/12	Gastro-enteritis	5·75	104	47·3
39	6/52	Gastro-enteritis	5·55	104	43·3
44	4/12	Gastro-enteritis	5·95	94	40·5
45	1/12	Gastro-enteritis	4·92	98	42·7
46	5/12	Gastro-enteritis	5·94	90	39·6
52	2/12	Gastro-enteritis	6·03	106	52·2
56	6/12	Gastro-enteritis	6·50	84	—
62	4/52	Pyloric stenosis	6·24	122	—
64	3/12	Gastro-enteritis	4·96	77	37·3
65	4/12	Gastro-enteritis	5·47	76	38·4
80	4/52	Pyloric stenosis	5·60	108	48·9
91	6/12	Gastro-enteritis	6·57	70	—
95	3/52	Pyloric stenosis	6·11	124	53·3
97	3/52	Pyloric stenosis	7·28	136	—
Average			5·95	99	44·7

The above children had received fluid parenterally before their blood was examined

TABLE 3

THE MOST EXTENSIVE CHANGES WHICH OCCURRED IN THE BLOOD IN DEHYDRATION

CASE	AGE	CLINICAL CONDITION	RED CELLS (MILLIONS PER C.MM.)	HAEMOGLOBIN (PER CENT.)	HAEMATOCRIT
2	8/12	D. and V. Otitis	6·00	92	46·7
8	3/12	D. and V.	5·60	112	45·5
9	8/12	D. and V. Otitis	5·42	104	41·1
10	3/12	D. and V.	5·88	112	45·5
16	5/12	D. and V. Otitis	8·27	126	56·7
17	3/12	D. and V.	7·27	120	56·7
20	3/12	D. and V.	5·89	105	46·5
21	9/52	D. and V. Old P.S.	5·43	102	47·8
27	8/12	D. and V.	6·68	107	48·9
28	6/52	D. and V.	5·30	108	—
33	6/12	D. and V. Otitis	5·75	104	47·3
34	3/12	D. and V.	5·30	92	43·2
35	6/12	D. and V. Anaemia	7·45	98	54·0
39	6/52	D. and V. Old P.S.	5·55	104	43·3
44	4/12	D. and V.	6·44	100	43·8
45	6/52	D. and V.	5·54	106	48·9
46	5/12	D. and V. Otitis	7·52	106	45·5
52	2/12	D. and V. Old P.S.	6·03	106	52·2
56	6/12	D. and V. Otitis	6·50	84	—
58	5/12	D. and V.	6·33	86	44·4
59	5/12	D. and V.	6·55	94	—
67	9/12	D. and V.	7·00	88	43·6
68	2/12	D. and V. Otitis	5·52	104	51·8
71	4/12	D. and V.	6·45	104	52·8
77	6/52	D. and V.	5·90	111	—
78	7/12	D. and V. Otitis	8·02	114	—
90	6/52	D. and V.	5·28	106	—
95	3/52	Pyloric stenosis	6·39	130	60·0
97	4/52	D. and V. Old P.S.	7·88	154	68·5
	Average		6·32	106	49·3

It will be seen that the average red cell count, both in those infants who had received fluid parenterally and those who had not, is well over 5 millions per c.mm. In compiling these tables the age of each individual was not considered, but the red cell count normally alters so much during the first six months of life that it is essential to know the age of the patient and the normal red cell count for that age before any opinion concerning the concentration of the blood can be given. The graph depicted in fig. 1 was obtained by plotting red cell counts against age in a series of normal healthy Birmingham infants, and represents the unpublished results of investigations carried out by Dr. M. B. Cleland at the Children's Hospital, Birmingham. The dots superimposed on this graph represent the red cell counts of dehydrated infants of the same ages at the time of their admission to hospital and are seen to fall above the normal black line. It is, therefore, clear that whereas a red cell count of 5·5 millions per c.mm. is normal in an infant aged four weeks, a similar count in an infant of three months of age suggests a fair amount of dehydration.

Haemoglobin concentration is also increased by dehydration, as is obvious in fig. 2, which was constructed in the same way as the graph of red cells. Since

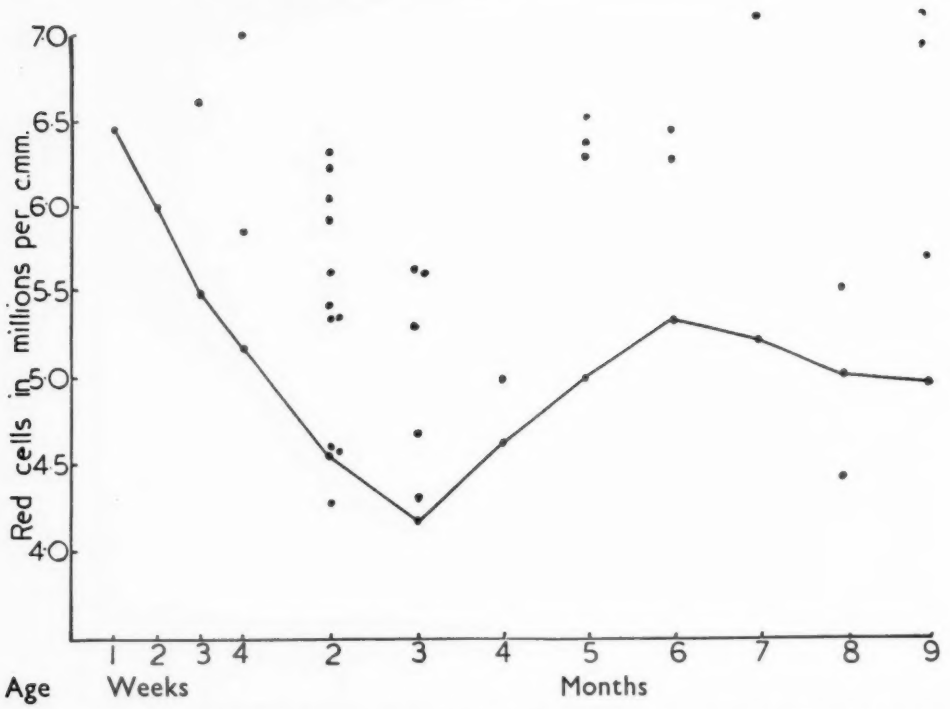

FIG. 1.—The continuous line represents the graph obtained by plotting red cell counts against age in normal infants. The dots represent dehydrated infants plotted in the same way.

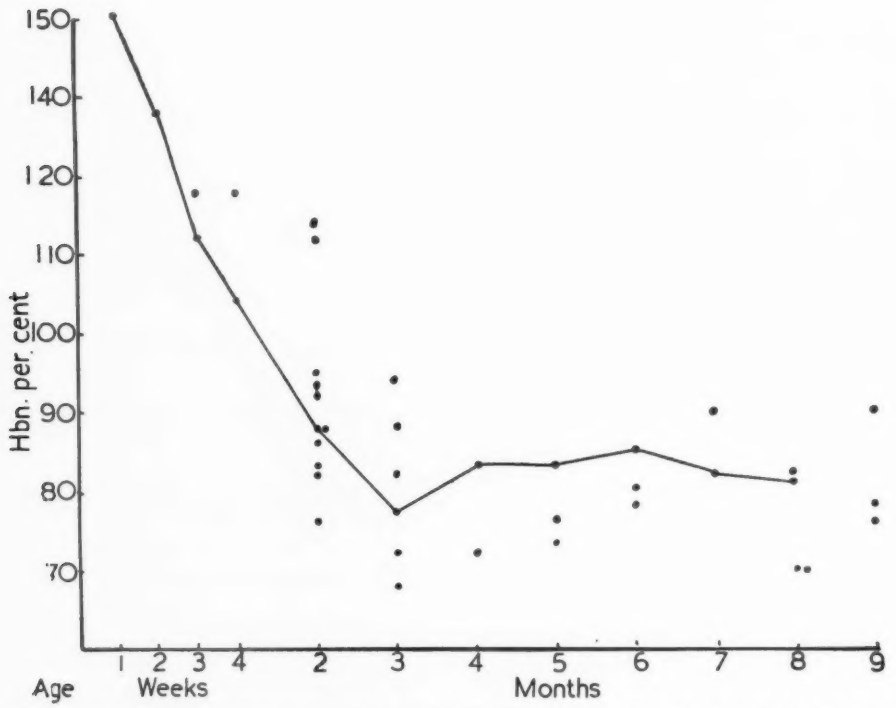

FIG. 2.—Haemoglobin plotted against age in normal (continuous line) and dehydrated (dots) infants.

many of the patients were suffering from hypochromic anaemia, the concentration of haemoglobin does not appear so marked as that of the red cells ; hence, estimation of haemoglobin alone gave quite an inadequate indication of haemo-concentration.

The average haematocrit readings (tables 1 and 2) were 44·9 and 44·7 respectively. These values do not appear to be raised much above the usually accepted normal figure of 42·0, but reference to fig. 3 (constructed in the same manner as fig. 1 and 2) shows that from the second to the eighth month normal readings are less than 38. Concentration by dehydration is, therefore, considerable. The range of readings obtained lay between 35·2 and 66·2, the

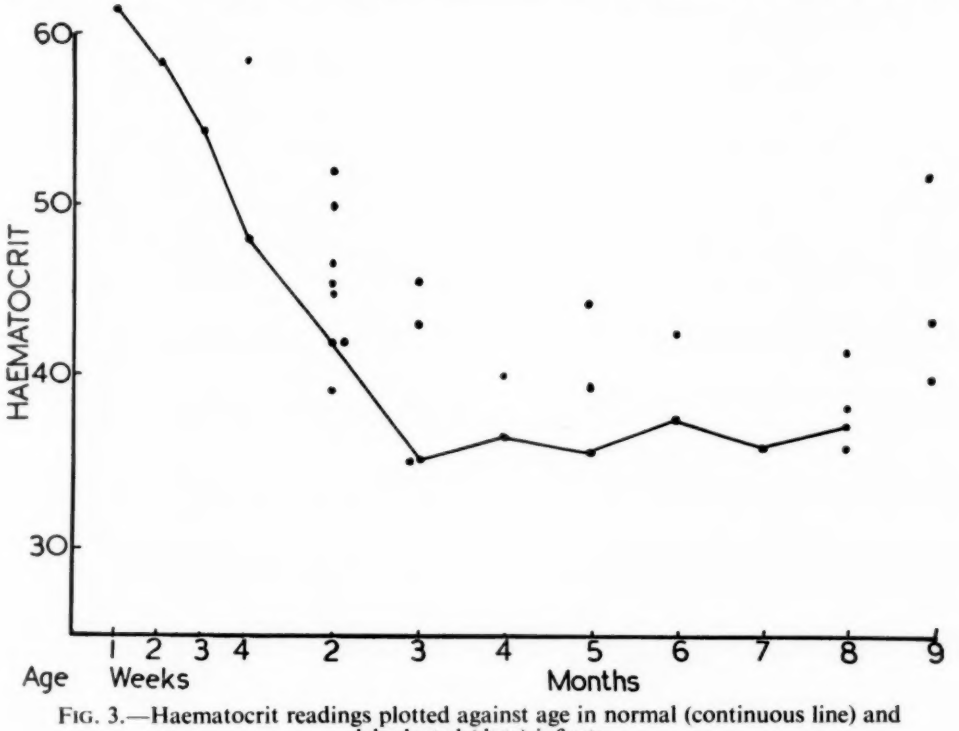

FIG. 3.—Haematocrit readings plotted against age in normal (continuous line) and dehydrated (dots) infants.

highest readings being found in dehydrated infants with pyloric stenosis. This finding is explained by the age of these patients : the oldest infant was twelve weeks old, the youngest three weeks, the average age of the fourteen cases being just over five weeks. At this age the normal red cell count is just under 5 millions per c.mm. and the colour index is still well over unity, so that the normal haematocrit reading is about 42·0. If a child of this age is dehydrated it is evident that the haematocrit reading will rise considerably above these normal figures. Actually, in the eight cases of pyloric stenosis examined, the average value was 52·7.

The lowest haematocrit readings occurred either in those children with gastro-enteritis who, whilst showing clinical evidence of dehydration, had little or no haemo-concentration, or in those who had well-marked hypochromic anaemia and resulting microcytosis.

In assessing the degree of haemo-concentration it is important to take into consideration whether nutritional anaemia is present or not, and this for three reasons : First, it has been shown by Parsons, Hickmans and Finch (1937) that in an iron deficiency anaemia the number of red cells may actually be increased to 5·5 or even 6 millions per c.mm., as the result of the anaemia alone ; secondly, the colour index may be reduced to 0·5, so that the haemoglobin concentration will be only half that expected for the particular red cell count ; thirdly, as a result of the microcytosis, even when an increased number of red cells occurs, the haematocrit reading may be low and remain within normal limits even when there is dehydration.

Chemical features

The values of plasma chloride and plasma protein found in a series of thirty-five infants with gastro-enteritis are set out in tables 4 and 5. Those examined before the administration of parenteral fluid are grouped together in table 4, whilst table 5 comprises those who had been given parenteral fluid before the estimations were done: this division is necessary because the fluid administered contained sodium chloride, and also because the concentration of plasma protein was presumably reduced by the administration of fluid which did not contain protein.

TABLE 4

THE CHEMICAL CHANGES IN THE BLOOD IN DEHYDRATION

CASE	AGE	CLINICAL CONDITION	PLASMA CHLORIDE (MGM. NaCl PER CENT.)	PLASMA PROTEIN (GRAMMES PER CENT.)
		Mildly dehydrated.	804	5·43
27	8/12	Mildly dehydrated. Otorrhoea (R. and L.)	687	7·11
28	6/52	Malnourished and dehydrated.	687	—
34	3/12	Very ill and dehydrated.	687	7·17
42	3/12	Looks dehydrated.	730	8·62
58	5/12	Mildly dehydrated.	614	7·06
59	5/12	Dehydrated and toxic. Poor colour. Cold.	629	6·61
66	7/12	Rather dehydrated. Otherwise good.	651	5·39
67	9/12	Very dehydrated, and toxic.	679	5·50
68	2/12	Mildly dehydrated. Pale.	678	4·96
69	9/12	Mildly dehydrated.	603	6·54
70	4/12	Dehydrated and pale. Severe diarrhoea.	537	6·83
72	2/12	Dehydrated. Poor tissue turgor.	581	7·72
73	3/12	Dehydrated. Very severe diarrhoea.	647	5·71
75	6/12	Dehydrated and toxic. Passing urine well.	536	8·74
76	10/52	Looks toxic. Not very dehydrated.	789	7·62
78	7/12	Extremely toxic and dehydrated.	672	8·17
90	6/52	Toxic. Poor turgor. Severe vomiting.	632	7·44
98	6/12	Dehydrated and toxic.	545	6·58
100	9/12	Dehydrated and toxic. Passing urine.	588	7·86
105	5/12	Very dehydrated and toxic-looking.	691	8·28
	Average		651	6·98

TABLE 5

THE CHEMICAL CHANGES IN THE BLOOD IN DEHYDRATION

CASE	AGE	CLINICAL CONDITION	PLASMA CHLORIDE (MGM. NaCl PER CENT.)	PLASMA PROTEIN (GRAMMES PER CENT.)
2	8/12	Dehydrated. Otitis. Vomiting marked.	674	7·70
4	5/52	Marked dehydration. Old pyloric.	750	—
14	6/12	Dehydrated and pale. Poor turgor.	628	—
17	3/12	V. dehydrated and ill. Previous B.T.	727	8·33
33	6/12	Dehydrated and ill. Pneumonia. Otitis.	716	7·76
39	6/52	Dehydrated and toxic. Old pyloric.	746	6·51
44	4/12	Looks v. dehydrated and toxic. Otitis.	818	7·23
45	1/12	Dehydrated. Poor turgor.	736	5·27
46	5/12	Mildly dehydrated. Otitis.	738	5·17
52	2/12	Dehydrated. Old pyloric stenosis.	753	6·38
56	6/12	Dehydrated and toxic. Severe diarrhoea.	820	6·98
64	3/12	Mildly dehydrated.	740	5·34
65	4/12	Very dehydrated. Pale.	696	4·67
91	6/12	Rather dehydrated. Pale.	651	5·75
	Average		728	6·42

All the cases in this table had received fluid parenterally before examination of the blood was carried out.

Plasma chloride. The amount of chloride in the plasmas of the twenty-one infants recorded in table 4 ranges from 804 mgm. to 536 mgm., the average being 651 mgm. per cent. These figures are considerably higher than those obtained from the series of normal infants, in which the average was 607 mgm. and the range 560 to 640 mgm. per cent. Consideration of the individual values shows that in eleven cases they were above 640 and in three below 560, whilst the remainder were within the normal limits. The height of the plasma chloride did not of necessity vary with the degree of dehydration nor with the clinical condition of the patient. For example, the highest reading of 804 mgm. per cent. was associated with only mild dehydration, whereas several children who were more dehydrated and worse clinically had under 600 mgm. per cent. of chloride in the plasma.

COMMENT. The observations of other workers on the chloride content of the plasma in dehydration also show that it may be high, normal or low. Some (Hartmann, 1928 ; Hoag and Marples, 1931 ; and Pincus and Kiser, 1931) found a large number of high values similar to those discussed above, whereas others (Darrow and Buckman, 1928 ; Hamilton et al., 1929 ; McIntosh et al., 1930 ; and Cooper, 1937) have reported a larger proportion of normal and low values. Boyd (1926) reports a series of sixty-six cases of acute intestinal intoxication of which thirty-three had normal chloride values, twenty-one were below normal and twelve above normal. In seven of her cases in which there was sudden, overwhelming toxaemia the average plasma chloride was 677 mgm.

per cent., whereas in cases of insidious onset the average was 590 mgm. per cent. She concludes that there is no definite relationship between the level of chloride in the plasma and the degree of toxaemia, and that the height of the plasma chloride is of no value in prognosis, which is not surprising when the number of factors affecting the chloride content is remembered. These factors may be considered under three headings :

LOSS OF ELECTROLYTES. When there is much loss of hydrochloric acid vomiting alone leads to alkalosis, a condition which is found especially associated with pyloric stenosis. On the other hand, diarrhoea alone tends to cause acidosis, since the intestinal juices are not reabsorbed and sodium and potassium are lost in the stools. A large amount of sodium chloride also may be lost in the stools in diarrhoea, although in health only small amounts are excreted by the bowel. The combination of vomiting and diarrhoea in gastro-enteritis may, therefore, lead to alkalosis or acidosis, either of which conditions may be compensated or uncompensated. In point of fact the greater loss usually occurs in the stools, so that vomiting does not materially affect the acidosis resulting from diarrhoea ; moreover, sick infants, especially those suffering from infections or nutritional disturbances, have a distinctly lower gastric acidity than normal infants, so that the amount of hydrochloric acid lost in the vomit is small (Marriott, 1923). In gastro-enteritis, therefore, the plasma bicarbonate is relatively lowered, because there is a loss of base, especially sodium, from the gut ; bicarbonate may be excreted with it or there may be a compensatory loss of CO_2 from the lungs. The amount of chloride as sodium chloride in the plasma is usually much less affected.

WATER DEFICIT. Dehydration affects all the tissues of the body. It has been estimated that when an adult shows signs of dehydration he has already lost fluid representing 6 per cent. of his body weight (Coller and Maddock, 1935). Although there is an attempt to maintain the blood volume at the expense of the tissues, there is, nevertheless, a loss of fluid from the circulation. This has been conclusively proved by many observers and is supported by my own figures. Marriott and Hartmann (1933) have drawn attention to the important point that the concentration of chloride and fixed base in the plasma may be normal or above normal in gastro-enteritis because, although these substances are lost from the body in considerable amounts, there is at the same time an even greater loss of water. The effect of this water loss may be enhanced by a diminished intake associated with vomiting and anorexia.

RENAL INSUFFICIENCY. Dehydration causes oliguria or even anuria. This affects the output of excretory products and electrolytes as well as water, so that the kidney is prevented from getting rid of excess acid radicles, of which the most important is the chloride. The significance of this renal insufficiency is stressed by Hamilton et al. (1929), Hartmann (1929), Marriott (1934), and Marples et al. (1934).

In summary, then, the relatively small loss of chloride as opposed to base, the concentration of the circulating blood and the renal deficiency are all factors in producing an apparent, if not actual, increased amount of chloride in the plasma in the gastro-enteritis of infancy. The plasma chloride, however, may

be high, normal or low according to the amount lost in the stools and vomit in relation to the water deficit.

Plasma protein. In considering changes in the plasma of dehydrated infants it is most important to remember that the normal values are less in the infant than in the adult. During the first eighteen months of life there is a gradual increase in the concentration of serum proteins until adult figures are reached (Peters and van Slyke, 1931). Normal figures for plasma protein are given as :

Albumin	3·4–4·9 grammes per 100 c.c.
Globulin	2·3–2·9 grammes per 100 c.c.
Total protein	5·6–7·5 grammes per 100 c.c.

With such widely differing values it is obviously difficult to gain much, if any, information concerning hydration of the blood from an isolated determination of plasma protein. To obtain a standard 156 estimations were carried out on the series of normal infants mentioned above, and an average figure of 6·31 grammes of protein per 100 c.c. of plasma was obtained. The highest value was 7·91 grammes per cent. and the lowest 4·77.

The values obtained in the series of dehydrated infants are set out in tables 4 and 5, those recorded in table 5 having received some sort of fluid parenterally before the blood was examined, which probably accounts for the lower values found in these children. The results are summarized in table 6, from which it will be seen that on an average the plasma protein in the dehydrated cases was a little higher than in a comparable group of normal infants.

TABLE 6

SUMMARY OF PLASMA PROTEIN VALUES IN NORMAL AND DEHYDRATED INFANTS

	NORMAL	DEHYDRATION	
		NO FLUID	AFTER FLUID
Average	6·31	6·98	6·48
Maximum	7·91	8·74	8·33
Minimum	4·77	4·96	4·67

COMMENT. The majority of observers agree that the plasma protein values are increased in dehydration, Marriott (1934) stressing the point that the plasma protein becomes concentrated as a result of a sudden acute loss of water and that when this anhydraemia has persisted for a few days decrease in the concentration occurs due to an actual destruction of protein ; nevertheless, some investigators have used the degree of plasma protein concentration to indicate the state of hydration of the circulating blood. In the present series of cases there was no definite relationship between the concentration of plasma protein and the red cell, haemoglobin and haematocrit readings, except that all these

values tended to be raised in dehydration. Many workers agree with these findings and hold that the estimation of plasma protein is an unreliable method of assessing the degree of hydration of the blood (Darrow and Buckman, 1928 ; McIntosh et al., 1930 ; and Marriott, 1934).

CHEMICAL FEATURES OF PYLORIC STENOSIS

Plasma chloride. The dehydration which occurs in uncomplicated cases of congenital hypertrophic pyloric stenosis is the result of fluid loss from vomiting because, owing to constipation, less fluid than normal is lost in the stools. A considerable amount of hydrochloric acid and sodium chloride is lost in the vomit, so that the plasma chloride falls, a fact demonstrated by Gamble and Ross (1924) in experimental pyloric stenosis in dogs, in one of whose experiments the following figures were obtained:

Before operation	613 mgm. per 100 c.c.
18 hours after operation	540 mgm. per 100 c.c.
29 hours after operation	473 mgm. per 100 c.c.
42 hours after operation	393 mgm. per 100 c.c.

According to Morris and Graham (1929), a low blood chloride is one of the most constant chemical findings in infantile pyloric stenosis, and at one time they held the view that the reduction of chloride bore some relation to the severity of the vomiting ; but in a later paper (1931) they stated that there might be a fall in the blood chloride during a prolonged absence of vomiting.

The plasma chloride values of a few cases of pyloric stenosis are shown in table 7. Five of these fourteen infants had received normal saline sub-

TABLE 7

THE BLOOD CHEMISTRY IN PYLORIC STENOSIS

CASE	AGE	CLINICAL CONDITION	PLASMA CHLORIDE (MGM. NaCl PER CENT.)	PLASMA PROTEIN (GRAMMES PER CENT.)
57	8/52	Dehydrated. Limbs cold and cyanosed.	521	6·51
62	4/52	Dehydrated. Poor turgor. Previous s.c. saline.	563	6·28
63	5/52	Condition very fair.	570	5·58
74	7/52	Condition quite good.	566	5·63
80	3½/52	Fair. Previous s.c. saline.	526	6·29
81	5/52	Fair. Previous s.c. saline.	569	6·58
83	4/52	Mild dehydration. Condition fair.	520	7·39
87	3/12	Dehydration mild. Condition poor.	547	5·63
88	5/52	Condition fair.	456	7·18
89	12/52	Dehydrated. Poor turgor.	555	5·51
94	4/52	Very dehydrated. Condition poor.	426	8·74
95	3/52	Fair. Previous s.c. saline.	529	6·38
96	7/52	Condition good.	427	5·61
97	3/52	Very dehydrated.	573	6·71
102	6/52	Condition fair. Mild dehydration.	552	7·02
103	5/52	Condition fair.	459	6·61
	Average		522	6·48

cutaneously (100 c.c. as a rule), but the remaining nine had had no fluid administered parenterally. Only five of these patients had values in excess of the accepted minimal normal figure of 560 mgm. per cent., and of these three had been given normal saline subcutaneously before the blood was examined. Thus, these figures, if not actually below normal were all on the low side of normal. Nowadays figures as low as those in Morris and Graham's series are not found because the diagnosis of pyloric stenosis is made earlier than formerly, usually within two or three days of the first attack of vomiting.

Plasma protein. The plasma protein values with an average reading of 6·48 grammes and a range of 8·74 grammes are slightly above normal, undoubtedly the result of dehydration.

CONCLUSIONS AND SUMMARY

The blood changes in a series of fifty-one infants showing varying degrees of dehydration (thirty-five suffering from gastro-enteritis and sixteen from pyloric stenosis) have been studied.

The red blood cell count was raised, the average count being well over 5 millions per c.mm., and it has been shown that this represents a considerable increase in the red count in infants of this age, although some of the increase may be due to nutritional anaemia. The haemoglobin was also increased, but often to a less degree than the red cell count because of the presence of hypochromic anaemia. Estimation of haemoglobin alone was not an adequate indication of haemoconcentration. When allowance was made for age and any nutritional anaemia that may have been present, the haematocrit reading was considerably above normal.

The plasma chloride in gastro-enteritis was variable, the average for the series was raised (651 mgm. per cent.), but in some cases the values were below normal. The height of the plasma chloride did not necessarily vary with the degree of dehydration or clinical condition. It was shown that an apparent, if not actual, rise in concentration of plasma chloride in gastro-enteritis and dehydration is due to:—(*a*) The relatively small amount of chloride as compared with base lost ; (*b*) the concentration of the circulating blood ; and (*c*) renal insufficiency. In pyloric stenosis the plasma chloride was either diminished slightly or on the low side of normal.

Plasma protein in gastro-enteritis was on the average a little higher than in a series of normal infants. The plasma protein concentration cannot be used as an indication of the state of hydration of the circulating blood. Plasma protein in pyloric stenosis was slightly above normal. In this series of cases no definite relation was found between concentration of plasma protein and blood cell, haemoglobin and haematocrit reading, except that all values tend to be raised above normal in dehydration.

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THE DIAGNOSIS AND CONSERVATIVE TREATMENT OF BRONCHIECTASIS IN CHILDREN

BY

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The title and purpose of this paper require some explanation. Its objects are to describe a method of bronchography in children, which has been tried at the Hospital for Sick Children, Great Ormond Street, and has been found to give an accurate picture of the bronchial tree. It also describes the conservative treatment by postural drainage, without, however, discussing the relative merits of conservative and operative treatment. It does not deal with the clinical diagnosis of bronchiectasis in children, which has already been described adequately in textbooks.

The authors feel, however, that postural drainage, whether used as a curative measure or in preoperative therapy, plays a most important part in the treatment of bronchiectasis in children. No apology is offered for calling attention to previous work, as many cases of bronchiectasis in children are being misdiagnosed and inadequately treated because this work has not been thoroughly understood.

The normal bronchial tree

Particular attention is called to the anatomy of the bronchial tree; for an intimate knowledge of this is essential to the production of good bronchograms that give a faithful picture of the nature and extent of the disease, upon which the correct postural drainage will depend.

Excellent diagrams of the bronchial tree in adults have been drawn by Nelson (1934), who has emphasized the importance of the anatomy both in the diagnosis and subsequent treatment of bronchiectasis. The anatomy of the bronchial tree is again discussed here. Contrary to many opinions the angles of the bronchi in children do not differ from those of adults.

Fig. 1 and 2 show:

1. That the right eparterial bronchus runs almost transversely, and then obliquely upwards.

2. That the right eparterial bronchus divides into three branches.

(a) **Apical,** running directly upwards.

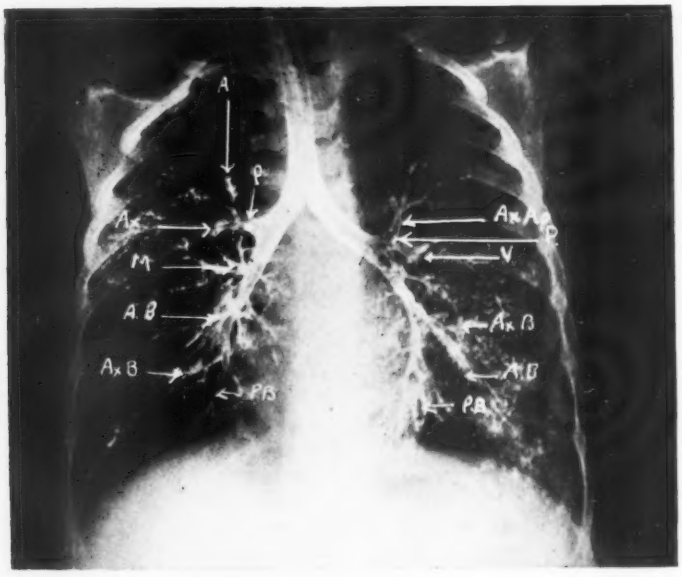


FIG. 1.—Anteroposterior bronchogram of both sides.

A=apical. Ax=axillary. P=pectoral bronchi. M=middle lobe bronchus. V=ventral bronchus. AB=anterior basic. AxB=axillary basic. PB=posterior basic bronchi and AxAp=axillary apical bronchus.

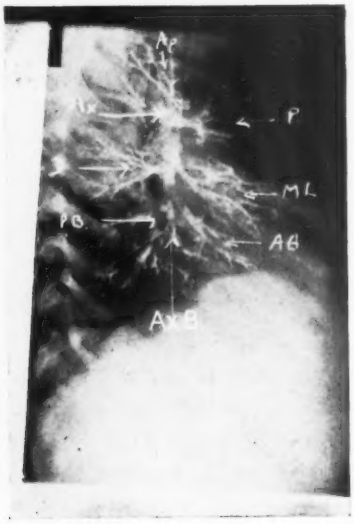


FIG. 2.—Right lateral bronchogram.

Ap=apical bronchus. Ax=axillary bronchus. P=pectoral bronchus. D=dorsal bronchus. ML=middle lobe bronchus. PB=posterior basic bronchus. AxB=axillary basic bronchus. AB=anterior basic bronchus.

(b) **Pectoral,** running forwards, downwards and slightly outwards.

(c) **Axillary,** running backwards, upwards and outwards.

3. That the right hyparterial bronchus supplies the middle and lower lobes, and divides ultimately into five branches:—

(a) **The right middle lobe bronchus,** running forwards, outwards and very slightly downwards.

Note the similarity in direction to the pectoral bronchus.

(b) **The dorsal bronchus,** arising at the same level as the right middle lobe bronchus and running horizontally backwards.

(c) **The anterior basic bronchus,** running forwards, and slightly downwards, parallel to the right middle lobe bronchus.

(d) **The axillary basic bronchus,** running downwards and outwards towards the costo-phrenic angle.

(e) **The posterior basic bronchus,** running downwards and backwards parallel to the right border of the heart.

Fig. 1 and 3 show the bronchial anatomy of the left side. It will be noted that it differs from the right side in the following ways:—

1. **The upper lobe bronchus** arises lower down, and at a less acute angle than on the right side. It is a branch of the left main bronchus and runs slightly forwards giving off the following branches:—

(a) **The axillary and apical,** which arise together and divide higher up into separate branches running in similar directions to those of the right side.

(b) **The ventral,** which corresponds to the middle lobe bronchus on the right, and runs forwards, outwards and slightly downwards.

2. **The lower lobe bronchus** divides into the dorsal, anterior, axillary and posterior basic branches. These have the same course and direction as those on the right side.

FIG. 3.—Left lateral bronchogram.

AxAp=axillary apical bronchus. V=ventral bronchus. D=dorsal bronchus. PB=posterior basic bronchus. AxB=axillary basic bronchus. AB=anterior basic bronchus. P=pectoral bronchus.

Technique of bronchography

The technique used at Great Ormond Street follows that described by Erwin (1936), Ellman (1939) and others.

PREPARATION OF THE PATIENT. It is essential that the bronchi should be as empty as possible before introducing the oil. This is achieved by providing postural drainage eighteen hours daily for one week. If this is not sufficient, drainage is continued for a further two to three weeks, or until the amount of sputum becomes negligible. Too much reliance must not be placed on the volume of sputum in children, as most of the sputum is swallowed. The best guides are the general condition of the child and the presence or absence of moist sounds on auscultation. The injection of oil is carried out while the patient is fasting, whether local or general anaesthesia is employed. But in the latter case the administration of atropine is essential. Considerable difference of opinion exists between the respective merits of general and local anaesthesia. The authors, after experience of both methods, have come to the conclusion that local anaesthesia is only advisable after the age of ten years, and even then, only in isolated cases. When using local anaesthesia the complete co-operation of the patient is essential, for he must neither cough nor swallow.

GENERAL ANAESTHESIA. At Great Ormond Street, induction with ethyl chloride, followed by deep ether anaesthesia has proved very successful.

BASAL ANAESTHESIA. Various forms have been tried in children, but they do not abolish the cough reflex, neither are the patients sufficiently co-operative. Jacoby and Keats (1938) advocate premedication with avertin, followed by ether anaesthesia.

LOCAL ANAESTHESIA. If this is used the patient must be tested for cocaine sensitivity. If the patient is not sensitive to cocaine, the larynx is anaesthetized by running 2 to 3 c.c. of a 1 per cent. cocaine solution through the syringe into the nose, using the technique employed for introducing the oil, shortly to be described. A better anaesthesia is obtained if the child sucks a decicaine sweet first. Two or three injections of cocaine are made over a period of twenty minutes to half an hour, the oil being introduced after a further interval of ten minutes. Jewesbury (1939) has suggested that laryngeal anaesthesia is unnecessary for bronchography, but it is impossible to obtain good results in children without it.

THE APPARATUS FOR INTRODUCING THE OIL. This is extremely simple, and consists of a tongue clip and a 10 c.c. record syringe to which is attached $1\frac{1}{2}$ inches of a $\frac{1}{10}$-inch bore rubber tubing.

THE IODIZED OIL. The preparation used was oleum iodisatum, B.P. addendum 1936, supplied by British Drug Houses. The oil is thinner than that commonly used and consequently flows easily from the nose into the larynx and trachea, producing better bronchograms in children, as the bore of the bronchi is small. The oil is used cold. The amount used varies with age and size of the child. To avoid superimposition of images of the bronchial tree in the lateral view, only one side is filled at one sitting.

If gross saccular bronchiectasis is suspected, much more oil will have to be used. The x-ray should be taken with the patient sitting up in the case of basal bronchiectasis.

DOSAGE

Age of child (years)	2–4	4–8	8–12
Volume required to fill one lung (c.c.) ..	3–4	4–6	6–8

Method of introduction of the solution. When the patient is fully anaesthetized, he is placed in the sitting position with the head held upright and chin forward. The patient's trunk should be inclined towards the affected side at an angle of 25 degrees to fill the right bronchial tree, and at 45 degrees for the left (fig. 4 and 5). The tongue is then grasped with a tongue clip applied 1 inch from the tip of the tongue and is held very firmly forwards. It is most important that the tongue should be held forward throughout, for if this is not

FIG. 4.—Position for filling the ventral, middle lobe and anterior basic bronchi.

done the aperture of the larynx is occluded by the base of the tongue and the oil merely runs into the oesophagus. The rubber catheter is then inserted for a half to one inch into the nostril of the side which it is required to visualize. 1½ to 2 c.c. of the solution are introduced. The patient should be kept in this position for fifteen to thirty seconds until the typical gurgle of the solution is heard as it passes between the cords. The success of the bronchogram now depends upon an accurate knowledge of the bronchial anatomy.

Fig. 4 shows the position for filling the middle lobe and anterior basic bronchi on the right side. A similar position is adopted to fill the ventral bronchus on the left side. Note that the head in this position is held extended. The patient

is flexed in this position and a further 1½ to 2 c.c. of the solution is introduced, and the position maintained for twenty to forty seconds. The patient is then returned to the sitting position (fig. 5) and ½ to 2 c.c. again introduced. When this has been done the patient is placed for twenty seconds in the semi-recumbent position leaning towards the affected side, in order to fill the dorsal, posterior, axillary and basic branches.

In children under general anaesthesia, the upper-lobe bronchi usually fill spontaneously, but if it is especially desired to fill them, two further positions are required. For the right side, after the bases have been filled, it is sufficient to turn the patient on his right side and to raise the pelvis. The left upper lobe bronchus is more difficult to fill. This is best accomplished by raising the pelvis

FIG. 5.—The inclination requisite for preventing the lipiodol from flowing into the other lung and should be held throughout the procedure.

and laying the patient on the left side, so that the left nipple is nearly in contact with the table. This last manoeuvre is necessary because the upper lobe bronchus on the left side runs slightly forwards, and gives rise to the ventral bronchus. This position therefore ensures that the ventral bronchus is filled.

The foregoing positions were elaborated by Erwin (1936) and others at the Brompton Hospital, and although they appear complex in description are easy to carry out.

This method of introduction is more suitable than the crico-thyroid route. For in children the landmarks in the neck are poorly defined, and the trachea is so easily compressed, that the introduction and maintenance of the needle in situ are difficult. Also in small children there is a danger of passing the needle right through the compressed trachea.

The simplicity of the apparatus and technique make this method ideal for hospitals with little experience of bronchography in children. A note of warning should be sounded about the amount of solution used, and the time allowed in each position; for if either of these two points are neglected, the solution will run into the alveolar spaces and obscure the picture of the bronchi.

Postural drainage

Nelson (1934) has placed on a sound footing the technique of postural drainage in relation to the anatomy of the bronchi. Unless stereoscopic views of the chest are taken, the clinician is apt to regard the child's chest as being a

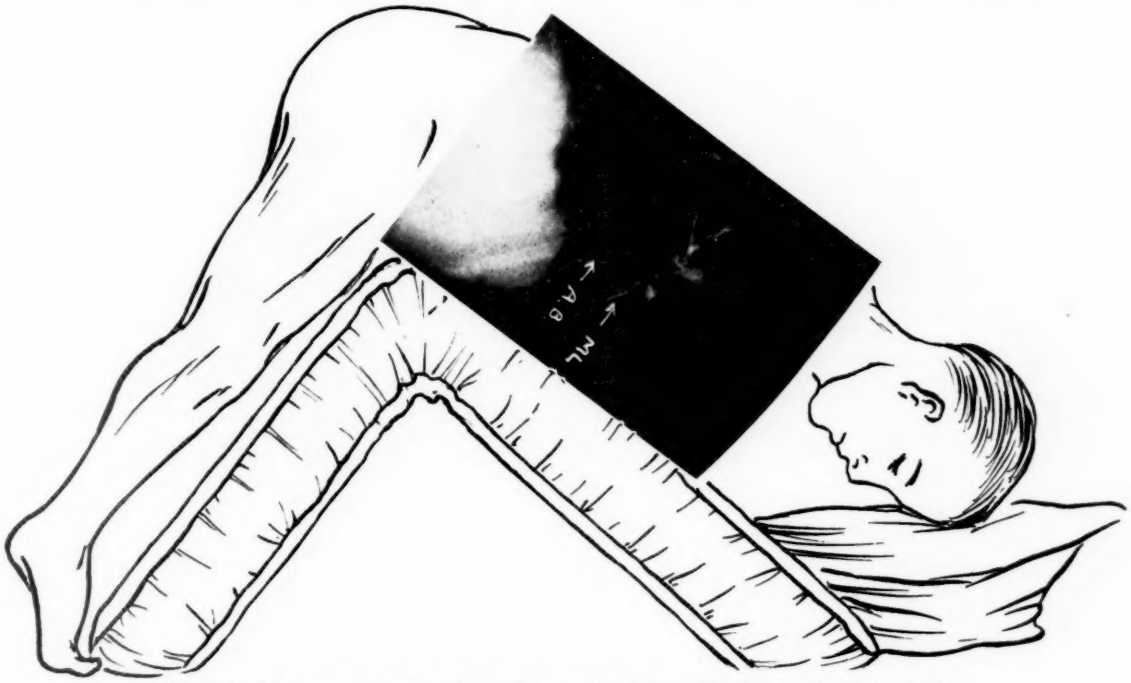


FIG. 6.—The *wrong* way to drain the middle lobe and anterior basic bronchi.

'slice' rather than a 'barrel.' In consequence the Nelson beds or tipping frames have been improperly used, for if a child is simply inverted on its face over one of these devices, the upper lobe, middle lobe and anterior basic bronchi remain undrained. Fig. 6 illustrates this. It is clear that it is useless to attempt to drain these bronchi against gravity.

Little attention has been paid to the rotation of the chest necessary for the optimum drainage of both middle and lower lobes. Wedges have been devised by one of us (B.E.B.) and are incorporated in a jacket in order to produce this effect; fig. 7, which shows a diagrammatic cross-section of a chest, makes this point clear. The maintenance of the position is the chief difficulty in securing postural drainage. If given the chance, children are seen happily straddling the tipping device during the day, or sleeping peacefully curled up at one or other end of the bed at night. The jacket into which the wedges may be inserted

allows some freedom of movement, while maintaining the necessary posture and rotation of the chest. Fig. 8 shows an ordinary strap jacket commonly used for keeping children in bed. To this have been attached two oblong pockets front and back, into which the wedges may be inserted. Two stock sizes of jackets and wedges are in use at Great Ormond Street, the sizes being given in the table below.

AGE (YEARS)	INCHES
2 to 6	$7\times4\times2$
6 to 10	$9\times5\times2\frac{1}{2}$

These are made of firm sponge rubber.

A strap like a martingale passes from the centre of the chest or back to the head of the bed, where it should be fastened so as to allow some freedom of movement. The feet should be tied loosely to the foot of the bed by straps attached to anklets of soft material.

Positions for drainage

1. THE UPPER LOBES in children can be drained by allowing them to run about; for it is difficult to keep the child in the ' Cleopatra position.'

2. THE MIDDLE LOBE, VENTRAL AND ANTERIOR BASIC BRONCHI. The child should be on its back on a flat bed with the chest raised by a wedge under the affected side. The foot of the bed should be raised eighteen inches to two feet. In this position it is essential that the feet be fixed to the foot of the bed by the method described.

3. THE AXILLARY BASIC, POSTERIOR BASIC AND DORSAL BRONCHI. To drain these bronchi the child should be placed on its face over a tipping device with the trunk at right angles to the legs. A wedge should be placed under the affected side. In this case it is essential to attach the martingale strap to the head, and the feet to the foot of the bed.

A word is necessary about the times required to drain the bronchi. The secretions are so viscous, that it is necessary for the patient to spend eighteen hours daily in the requisite postures while in hospital, and the entire night when at home. Should the basic and middle lobe or ventral bronchi be affected together, the time should be divided equally between the two postures.

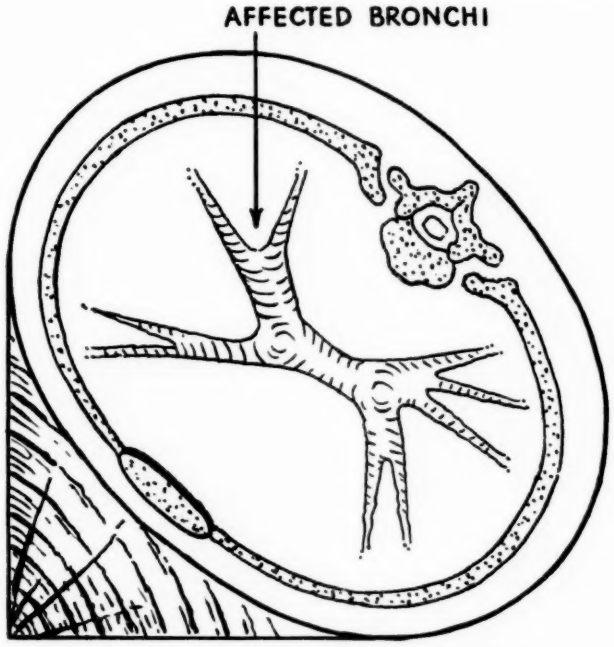
Finally, it is always advisable to give a liquefying expectorant mixture during the course of postural drainage. Both the Brompton Hospital hot-water mixture

℞ Sodium bicarbonate	20 grains.
Sodium chloride	3 grains.
Emulsion of chloroform B.P.C.	5 minims.
Syrup of anise B.P.C.	3 minims.
Distilled water to 1 fluid ounce.	

or the Hospital for Sick Children, Great Ormond Street, Mist. senegae ammon.

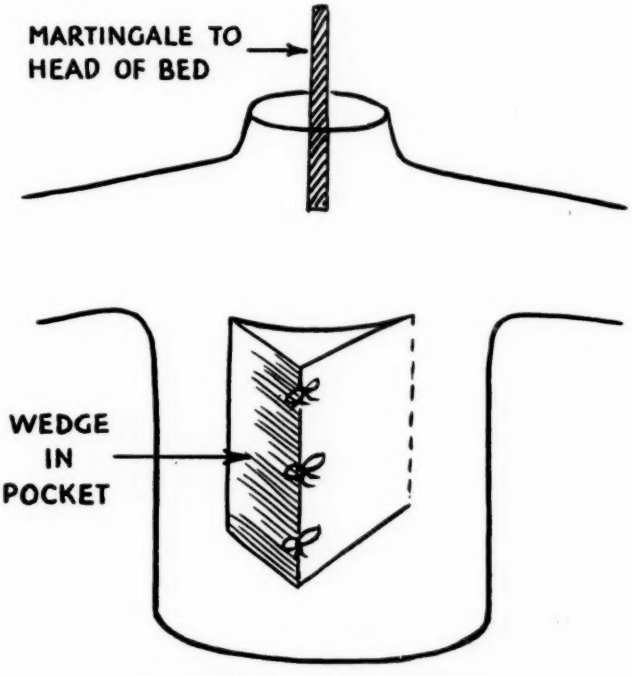
℞ Ammonium carbonate	½ grain.
Spirit of chloroform	2 minims.
Syrup	15 minims.
Inf. of senega to 60 minims.	

are efficacious.



SHOWING WEDGE MAINTAINING THE BRONCHI TO BE DRAINED UPPERMOST

FIG. 7.



STRAP JACKET SHOWING MARTINGALE AND WEDGE

FIG. 8.

Summary

1. The anatomy of the bronchi is discussed in relation to the technique of bronchography.

2. The technique of bronchography for children is given in detail.

3. Postural drainage in children is discussed, and particular attention is called to the methods of maintenance of posture.

Thanks and acknowledgments are due to the Honorary Staff of the Hospital for Sick Children, and also to the Photographic and Pharmaceutical Departments for their kind co-operation.

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INFANTILISM, OBESITY AND RETINAL DYSTROPHY

A ' Forme Fruste ' of the Laurence-Moon-Biedl Syndrome

BY

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In 1866 Laurence and Moon reported ' Four cases of " retinitis pigmentosa " occurring in the same family and accompanied by general imperfections of development.' These imperfections included small stature, hypogenitalism, obesity and mental defect, although little emphasis was placed on the two last. Over fifty years later, Bardet (1920) added polydactyly to the syndrome, and in 1922 Biedl, reporting three new cases, emphasized the familial character of the syndrome, the occurrence of mental defect and the occasional association of other abnormalities.

Comprehensive reviews of the literature have been made by Raab (1924), Reilly and Lisser (1932), Cockayne, Krestin and Sorsby (1935), Streiff and Zeltner (1938), and Sorsby, Avery and Cockayne (1939). Reilly and Lisser found seventy-seven cases, of which they regarded twenty-five as complete examples of the syndrome, ten as questionably complete, twenty-seven incomplete and fifteen doubtful. Sorsby et al. discussed a number of allied conditions, including Biemond's (1934) syndrome (familial infantilism, coloboma of the iris and skeletal abnormalities) and Cockayne's (1936) syndrome (familial dwarfism, mental deficiency, deafness and retinal atrophy), but regarded the Laurence-Moon-Biedl syndrome as clear-cut and distinct. Warkany, Frauenberger and Mitchell (1937), however, put forward the view that the syndrome is not a disease entity but ' a rare combination of more or less frequent heredofamilial symptoms.'

According to Marmor and Lambert (1938) the six cardinal signs of the syndrome, in order of their frequency, are obesity, retinitis pigmentosa, mental deficiency, genital dystrophy, familial incidence and polydactyly, the last occurring in approximately 60 per cent. of cases. Less common signs are dwarfism, syndactyly, deafness, atresia ani, oxycephaly and congenital morbus cordis.

Although the term ' retinitis pigmentosa ' has generally been used to describe the retinal changes, in only 15 per cent. of cases (Clay, 1933) do these conform with the classical picture of retinitis pigmentosa. In the great majority of instances they have been ' atypical ' or have even differed profoundly in essential features. Sorsby (1940) considers that ' the significance of the affection in the elucidation of the pathology of retinitis pigmentosa has been overrated, for the fundus lesion is not generally a typical pigmentary degeneration of the retina. ' Atypical ' retinitis pigmentosa is the rule, and occasionally the lesion is essentially a macular dystrophy with optic atrophy.'

In the case reported below, the fundus lesion differed essentially from that of retinitis pigmentosa, but we have little hesitation in classifying the case as a ' forme fruste ' of the Laurence-Moon-Biedl syndrome, in view of the infantilism and obesity and of the occurrence of mental defect and polydactyly in members of the immediate family.

Case report

Monica M., a girl aged thirteen years and three months, attended the Royal London Ophthalmic Hospital in April, 1940, on account of defective vision, and because of her small size was subsequently transferred to Guy's Hospital (later to the Kent and Sussex Hospital) for further investigation.

FAMILY HISTORY. Both parents are of normal stature and are unrelated. The father is alive and well, and the paternal grandparents were normal ; a younger brother of the father, who was drowned, had very defective vision, but was otherwise normal.

Of the maternal forebears, the patient's grandmother died from pulmonary tuberculosis and the grandfather from angina pectoris. The patient's mother has suffered from open tuberculosis and had artificial pneumothorax treatment. Ophthalmic examination of the mother showed : vision, right 6/6, left 6/6. No nystagmus present ; fundi normal.

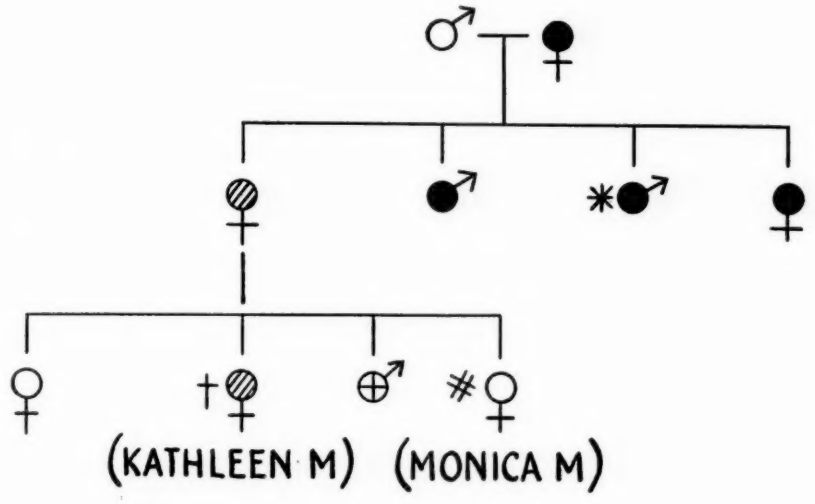
The mother's two brothers and one sister all died from pulmonary tuberculosis. The younger of the two brothers had a sixth digit on the radial side of the right hand.

The patient has two elder sisters, and a brother who died at birth. One sister, aged twenty-five, is normal. The second sister (Kathleen M.), aged twenty-three, is mentally defective and has suffered from chronic fibroid phthisis for the past eight years. She is at present in a sanatorium, where she was examined by one of us (R. W. B. E.). During infancy she suffered from spasmus nutans. She was late in walking and talking, and did not learn the alphabet until twelve years old. She began to menstruate at sixteen ; menses are now regular. Her eyesight has been defective for at least ten years. On examination, she is below the average height, being 5 feet (152 cm.) tall ; she weighs 102½ lb. The circumference of head is 19⅞ inches. The fingers are clubbed, and there are signs of extensive fibrosis at both apices. Secondary sexual characters and genitalia are normal. She is of defective mentality, but understands simple requests and is cheerful and co-operative. She can read, but holds print very close to her eyes. She does not appear to suffer from night blindness. There is no nystagmus. The optic discs are a deeper colour than normal, but are well defined. The vessels are normal. There is no abnormal pigmentation of the retinae.

PERSONAL HISTORY (Monica M.). The patient was born at term, weighing 8 lb. ; delivery was normal. At birth she is said to have had a thick growth of hair on the head which extended posteriorly on to the dorsal region ' like a pigtail.' She gained poorly in weight during the first year, and has always been small for her age since then. She walked and talked early, and cut her first tooth at six months old. Obesity has developed gradually over a period of several years and more rapidly recently. Her general health has been good, and measles and influenza are the only illnesses she has had.

During the past twelve months her eyesight has rapidly deteriorated. She frequently trips over the curb and cannot see the markings on a ruler. There have been no headaches, and she has not suffered from polyuria, excessive thirst or frequency.

At school she is slightly above the average, consistently being placed amongst the first four in a large class of girls of her own age.



●—DIED TUBERCULOSIS
◍—ACTIVE TUBERCULOSIS
✳—POLYDACTYLY
†—MENTAL DEFECT
✳—INFANTILISM AND RETINAL DYSTROPHY
⊕—DIED AT BIRTH

Examination (June, 1940). A bright, co-operative little girl, who, whilst normally intelligent for her age, tends to have the emotional reactions and interests of a considerably younger child. She measures 45½ inches (115·5 cm.) in height, i.e. the same as a normal child of seven years, and weighs 61½ lb. (The average figures for a normal girl of thirteen-and-a-quarter years are 59½ inches and 92 lb.) Other measurements are: sitting height 23½ inches, circumference of head 20 inches (normal 21 inches), chest (nipple level) 26 inches, abdomen (umbilical level) 26½ inches, around midgluteal region 28 inches, length of arm (acromion to radial styloid) 13½ inches, hand (radial styloid to tip of middle finger) 4½ inches, leg (anterior superior iliac spine to internal malleolus) 24½ inches, from umbilicus to ground (standing) 26⅝ inches.

THE FACIES is that of early childhood, the nose and maxilla showing no sign of the development normally associated with the onset of puberty.

THE SKIN is fine and smooth over the face and greater part of the trunk, but there is some hypertrichosis over the back, particularly in the mid-line, and over the extensor surfaces of the forearms. There are no striae atrophicae. The colour is normal. The hair is moderately abundant, silky, and brown ; the eyebrows and eyelashes are black, and of normal distribution.

OBESITY. The distribution of fat is principally of ' girdle ' type, though the whole of the trunk is involved. The extremities are affected less in the proximal than the distal segments ; the hands and feet are small, and the fingers tapering (figs. 1, a and b).

DENTITION. Teeth present:

6E4C21	12C4E6
6EDC21	12CDE67

Radiological examination shows that the unerupted teeth are normally present.

SEXUAL CHARACTERS. There is no axillary or pubic hair, and no mammary development. The nipples are retracted, owing to the deposition of fat in the

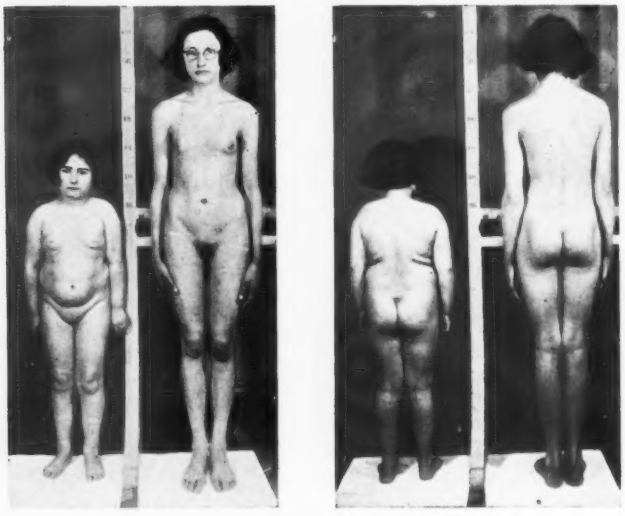


FIG. 1, a and b.—Monica M. with normal control, aged $13\frac{1}{4}$ years. Anterior and posterior views showing brevilinear proportions, infantilism, and distribution of obesity.

mammary region, and there is no pigmentation of the areolae. The genitalia are infantile.

Ophthalmic examination. VISUAL ACUITY. The patient was first seen in April, 1940, complaining of defective vision. Visual acuity was found to be: right, 6/24; left, counts fingers at 2 feet. Refraction under atropine was carried out and the following results obtained:

Right $-1{\cdot}5$ D.S. $+2{\cdot}0$ D.C.$-150^\circ = 6/12$ partly.
Left $-1{\cdot}0$ D.S. $+1{\cdot}0$ D.C.$-45^\circ = 6/18$.

Two weeks later a postmydriatic test was carried out, when the same glasses produced only 6/18 in the right eye and again less than 6/60 in the left. On re-examination in July, on which occasion she had failed to bring her glasses, it was found to be, unaided, right 6/24, left 6/36. Such a variable subjective result is not uncommon in patients, especially children, suffering from nystagmus, and is probably dependent on the frequency and amplitude of the oscillations, these in turn possibly being influenced by psychological and nervous factors.

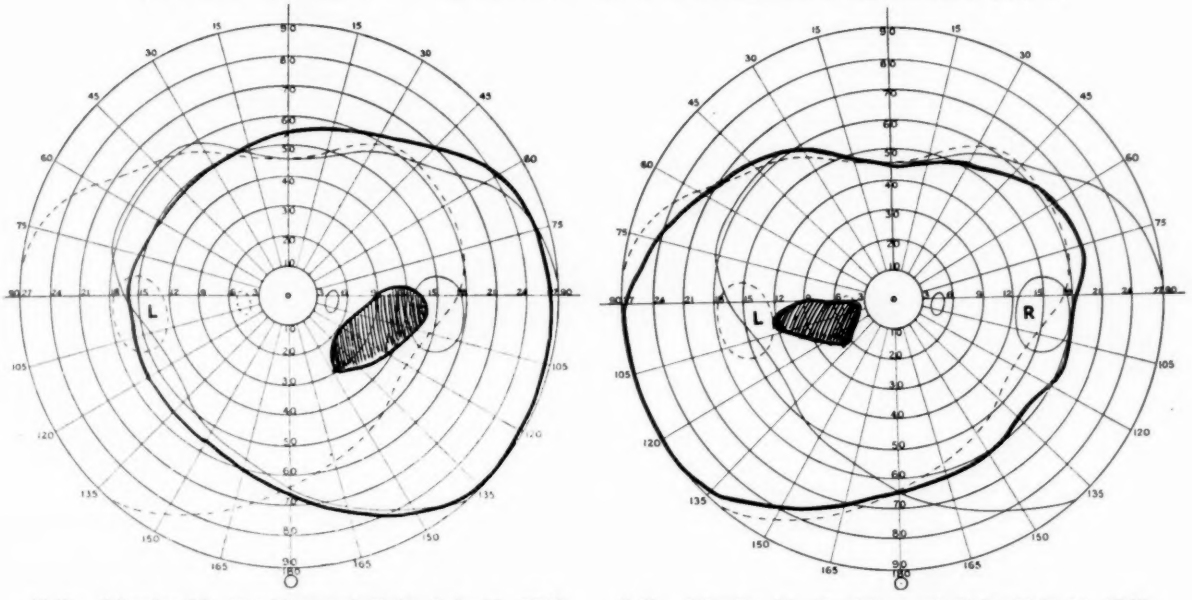
As regards the child's description of her own vision, she stated in April that she suffered from defective vision in the dusk. This she now denies; indeed, when evacuated ten months ago she wrote to her mother and volunteered the information that her vision was improved in a dim light. Whatever her subjective sensation, there is no discoverable clinical evidence of abnormal variation of visual acuity in varying illumination.

EXTERNAL EXAMINATION. There is (July, 1940) a constant fine nystagmus of the type usually associated with defective macular vision, perhaps better termed defective fixation than true nystagmus. The movements are in the vertical meridian and consist of a quick rising phase and slower regular fall. In addition to this there is a coarse horizontal nystagmus on deviation to right or left, the phases being approximately equal. Pupillary movements are normal and there is no external abnormality.

VISUAL FIELDS. Response to this test was very willing and co-operative, but the results must be read in the light of the defective fixation present. There is no peripheral field loss to a 1° object at 330 cm.; the blind spots, however,

appear to be enlarged (fig. 2, a and b). It is obvious that delicate scotometry was impossible.

FUNDUS EXAMINATION. Gross atrophic changes are evident, of which an indication is given in the two monochrome drawings here reproduced (fig. 3,



R.E. Monica M. 1° white, artl. light, July 11, 1940. L.E. Monica M. 1° white, artl. light, July 11, 1940.

FIG. 2, a and b.—Right and left visual fields.

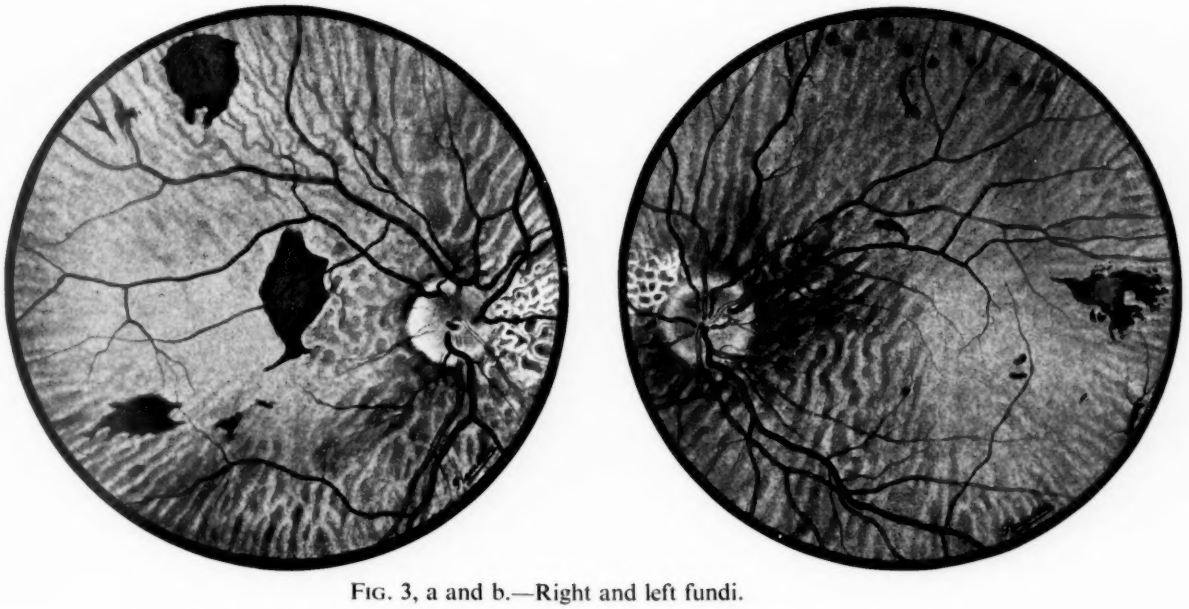


FIG. 3, a and b.—Right and left fundi.

a and b). These, however, were made under difficult conditions, and must not be taken to represent a completely accurate picture. The discrepancies may be deduced by comparing the description of the fundi with the drawings.

The two most obvious features on ophthalmoscopic examination are the

easy visibility of the choroidal vessels and the presence of plaques or ' veils ' of pigment scattered over the fundi. The retinae appear ' thin ' and there is evident general deficiency of pigment throughout. The choroid itself is not heavily pigmented either, and, as already mentioned, the choroidal vascular system is plainly seen. The macular regions are atrophic and ' moth-eaten ' in appearance; there is fine scattered peppery pigmentation at the left, but the right area is the actual site of one of the plaques in addition. (This point is not brought out in the drawing).

The plaques or ' veils ' of pigment which are unevenly scattered over both fundi vary in size, some being nearly as large as two discs. Their depth is difficult to assess, but is estimated as being about that of the retinal vessels. Their outlines are quite irregular; their density is fairly constant, underlying structures not being entirely obscured.

There is no definite change in the appearance of the vessels or optic discs. The fundus picture may be summed up as showing retinal atrophy with pigment migration and macular degeneration; there is not the slightest ophthalmoscopic or clinical resemblance to retinitis pigmentosa.

Radiological examination. SKULL. There is no evidence of raised intracranial pressure or other abnormality. The pituitary fossa is normal, and there is no erosion of the clinoid processes.

OSSIFICATION. The ossification centres of the carpus are normal for age, except that the pisiform is not visible. At the elbow, the centre of ossification of the olecranon process of the ulna is just visible. Those of the trochlear and of the internal epicondyle of the humerus are well developed, but that of the external epicondyle has not appeared. Ossification, therefore, appears to be slightly delayed for age (i.e. that of a child of eleven or twelve), but not to the extent that the size of the patient might suggest.

CHEST. The hilar shadows are enlarged, but there is no evidence of active pulmonary disease.

Other investigations. WASSERMANN and KAHN reactions negative.

MANTOUX TEST (1 in 10,000 dilution) strongly positive.

BLOOD UREA. 34 mgm. per cent.

UREA CONCENTRATION TEST (15 gm. urea):

TIME	URINE, C.C.	UREA, PER CENT.
7 a.m.	73	2·12
8 a.m.	43	2·38
9 a.m.	94	2·87

FLUID INTAKE averaged 18 oz. (540 c.c.) daily over a three-day period.

URINARY OUTPUT averaged 24 oz. (720 c.c.) daily over a three-day period.

URINE contained faint trace of albumin, but no other abnormality. Specific gravity 1012.

STOOL examination showed no excess of faecal fat.

Discussion

In discussing the etiology of the condition, Sorsby et al. drew attention to ' the frequent occurrence of one or more components of the Laurence-Biedl syndrome in the ascendants of patients showing the full syndrome,' and suggested that the syndrome is ' determined by two recessive genes in the same chromosome, or that it is dependent on some chromosome error such as a dislocation or translocation.' In so far as information is available with regard

to the presence or absence of consanguinity, the complete sibships published indicate the recessive character of the condition; thus, in the fifty sibships in which a definite statement is made, 20·4 per cent. were the result of marriages between first cousins and 38·7 per cent. the result of consanguineous marriages.

The present case, an incomplete example of the full syndrome, was the offspring of unrelated parents, but the features of the syndrome which were lacking in the one individual, viz. mental defect and polydactyly, were found in a sister and uncle respectively. The patient herself was a singularly perfect example of infantilism associated with obesity, and though her intelligence was normal for age her emotional development was commensurate with her physical state. An unusual feature of the polydactyly present in the uncle was that the extra digit appears to have been situated in the preaxial position, whereas in previously reported cases it has been postaxial. As, however, the affected patient is dead, and no photograph is available, this point cannot be confirmed from personal observation.

A further point of interest in connexion with the patient, Monica M., arises from a consideration of the actual type of retinal atrophy present, and its ophthalmoscopic appearance. The term 'retinitis pigmentosa' is pathologically and descriptively unfortunate for any known ophthalmoscopic condition; when it is applied to the retinal changes found in conditions such as the one under consideration it is unjustifiable, since there is no evidence that the retinal condition bears any fundamental relationship to that usually referred to by this name, and the case provides good ophthalmoscopic evidence of a lack of relationship. The recurring use of the term 'atypical' in the writings quoted is significant.

The original description by Laurence and Moon reads as follows: 'Scattered over the fundus oculi, but especially aggregated towards its periphery, were several irregular figures of deep black colour. None was visible either in the situation of the macula lutea or its immediate neighbourhood. Their forms were exceedingly various, some being flakes or streaks of pigment, whilst others appeared as black oblong or oval spots, with fine dark lines extending from them, very closely resembling bone corpuscles in shape.

The pigment spots were apparently situated in the substance of the retina, on a level with its vessels, in some places interrupting these in their course and at others running for a short distance closely by their sides. They were distinctly on a plane anterior to the choroid. The vessels of this latter structure could everywhere be most beautifully seen, even to the minutest ramifications, excepting at those parts where the pigment obscured them from view. The spaces between these vessels were of a paler colour than the vessels themselves.

Each optic papilla was of a reddish-pink colour, with a rather brightly stippled centre; its margin softly defined, surrounded by a pale zone.'

Cockayne et al. summarized the ophthalmoscopic appearance thus: 'Typical retinis pigmentosa is recorded . . . Atypical retinitis pigmentosa is noted . . . The atypical forms range from small chorioretinal lesions . . . from peripheral pigmentary lesions . . . sparing the macula to a lesion involving the macula . . . from retinitis pigmentosa sine pigmento to atypical retinitis punctata albescens . . . Typical retinitis pigmentosa would appear to be the exception.'

The paper by Laurence and Moon is a careful and very valuable piece of work, but was written over seventy years ago, and an improved terminology might to-day be justifiably substituted; anticipatory permission for this is indeed then given by the authors: 'In calling these cases by the name of Retinitis Pigmentosa, we have been guided rather by usage than by the intimate nature of the cases.'

As has been already stated, there is no resemblance between the fundus appearances in the present case and those of 'typical retinitis pigmentosa,' nor is the subjective disturbance of vision compatible. The more obvious differences in appearance may be summed up as follows:

1. The pigment disturbance and distribution is atypical.
2. The vessels are not constricted.
3. The discs are not of the pale yellowish colour found in typical cases.
4. The choroidal vessels are rarely seen in a typical case as clearly as in ours, at least in the early stages.

It is interesting to note that, whereas there are such wide variations in ophthalmoscopic appearances in cases of this syndrome, the description in the original paper of the first case might well be applied to the present one. Amongst other points of resemblance, the clear visibility of the choroidal vessels is emphasized, and Laurence and Moon's term 'flakes' and the use here of the term 'veils' in describing the pigment patches suggest similar pictures.

In considering the ophthalmoscopic picture, no less than the general clinical one and family history, we have no hesitation in placing our case in the Laurence-Moon-Biedl category.

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DESOXYCORTICOSTERONE ACETATE AND OESTRADIOL DIPROPIONATE THERAPY IN THE NEWBORN INFANT

BY

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(From the Royal Infirmary, Edinburgh)

This paper is devoted to the study of oestrogenic and adreno-cortical action upon the gastric acidity and weight progress of the infant during the first ten days of life. It is known that the influence of the hormone oestrin upon the growth of the premature infant, more particularly in girl babies, is stimulating (Moncrieff, 1936; Potter, 1937). Its action upon the gastric acidity, however, has only been observed in adults, in whom no difference could be detected by Atkinson (1939) or Sandweiss et al. (1939). The influence of desoxycorticosterone acetate in infancy has not been recorded, and Bruch and McCune (1936) did not consider such therapy was indicated. Nevertheless, a degree of adrenal insufficiency may be present as there is a haemoconcentration, and a raised non-protein nitrogen and serum protein during the first days of life, as well as involution of the suprarenal gland.

Investigation

The behaviour, weight, progress, and gastric secretion of sixty babies has been studied during the first ten days of life. The infants were divided into three groups of twenty, with an equal number of girl and boy babies in each. The purpose of having groups was to keep one as a control, while the others were treated with either oestradiol dipropionate (Ovocyclin-P) or desoxycorticosterone acetate (Percorten). The oestradiol compound was chosen because its potency is far greater than that of oestrin, theelin, emmenin, trihydroxyoestrin or ketohydroxyoestrin which have been used for similar investigations. The dose was 1 mgm. intramuscularly on the first day of life, and it was repeated on the fourth day in ten of the cases. Percorten was also given intramuscularly, but on the first, fourth and eighth days of life, the dose being 5 mgm. on each occasion.

The gastric acidity was investigated on the second, fifth and seventh days of life after the infants had been starved for seven to eight hours. The fasting

* Working under the auspices of the Kirk Duncanson Fellowship for Medical Research, The Royal College of Physicians, Edinburgh.

juice was first withdrawn and then a test-meal was given. It consisted of equal parts of breast-milk and water and amounted to one drachm per pound body weight. After the meal three specimens of gastric contents were taken at half-hourly intervals, except in the group of infants treated with desoxycorticosterone, in whom the last specimen was omitted. When possible, 1 c.c. of each sample was quantitatively analysed for free and total acidity by titrating it with N/70 NaOH from a microburette. The end point of the titration was determined with Topfer's reagent and phenolphthalein as indicators.

The results of the total acidity are expressed in c.c. N/10 HCl per 100 c.c. gastric contents, and recorded in fig. 1. The only significant difference between

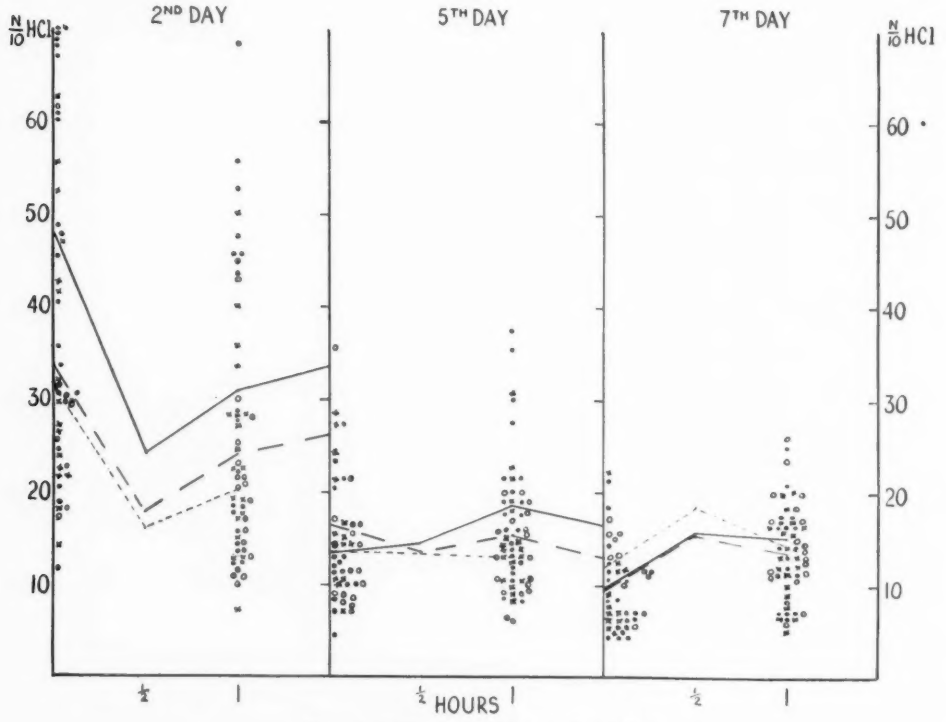

FIG. 1.—To show the total acidity

Continuous line represents average for control group.
Coarse interrupted line average for oestradiol group.
Fine interrupted line average for Percorten group.
Dots indicate individual readings in control group.
Crosses indicate individual readings in oestradiol group.
Circles indicate individual readings in Percorten group.

the curves for total acidity in the three groups is the higher acidity for the control group on the second day of life. This is probably a coincidence arising from the great variation in the total acidity during the first two days of life. It is not evidence that the hormones lower the acidity, as the difference does not persist throughout the first week of life. The average values for free acidity are given in table 1, where they are expressed in c.c. N/10 HCl per 100 c.c. gastric contents. The brief account suffices, for the free acid was only

present on the second day of life. This is not surprising, as the free acid does not usually appear unless the total acidity exceeds 30 c.c. N/10 HCl, and this only occurred three times on the fifth day and once on the seventh day of life.

TABLE 1

GROUP	FASTING JUICE	½ HR. P.C.	1 HR. P.C.	1½ HR. P.C.
Control	18·3	0·2	2·5	3·7
Oestradiol..	8·8	0·6	0·8	5·0
Percorten	5·1	0·7	1·5	—

The influence of the hormones upon the total acidity of the two sexes is demonstrated in fig. 2. In it an equal number of male and female infants

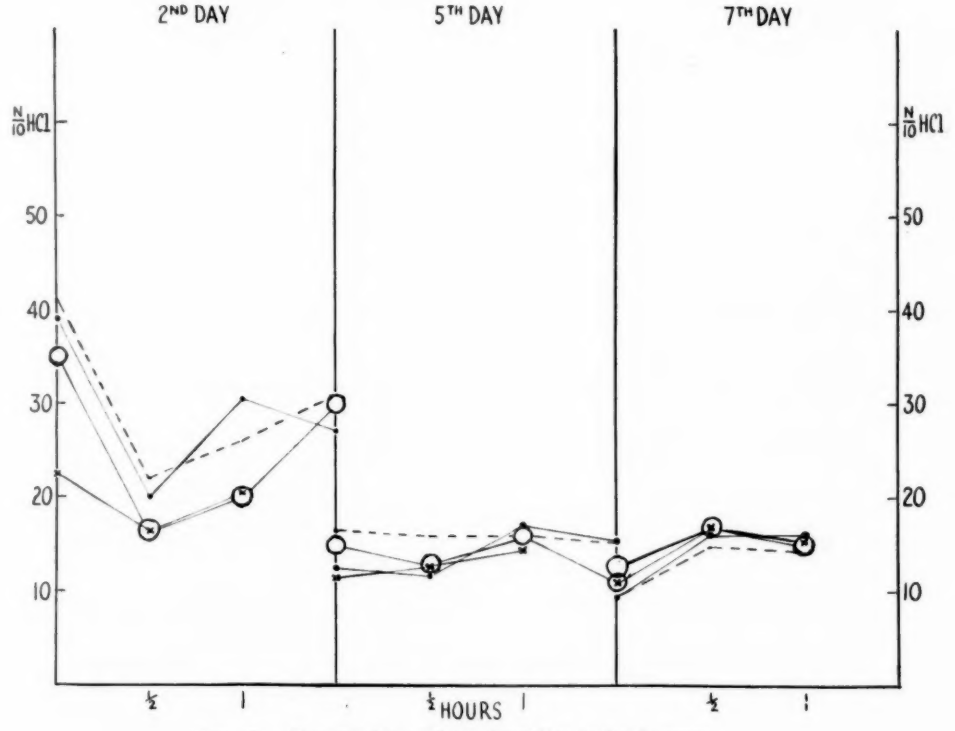

FIG. 2.—Comparison of total acidity in both sexes

Dot represents female control group.
Circle represents female oestradiol group.
Cross represents female Percorten group.
Interrupted line represents all male infants.

are compared in each group. The gastric acidity does not vary with sex or with hormone therapy during the first week of life; it does not therefore behave as in older infants, since the male is supposed to have a more acid secretion than the female (Tomotake, 1930).

The effect of hormone therapy upon weight progress. The progress of all the infants was carefully watched and test-feeds given periodically, so that underfed babies might have any deficiency remedied. Their weight progress was not retarded by ill health, although one infant was jaundiced and two suffered from upper respiratory infections, from which no systemic disturbance was noted. The percentage loss of birth weight of the three groups during the first ten days of life is contrasted in fig. 3. The average birth weight of

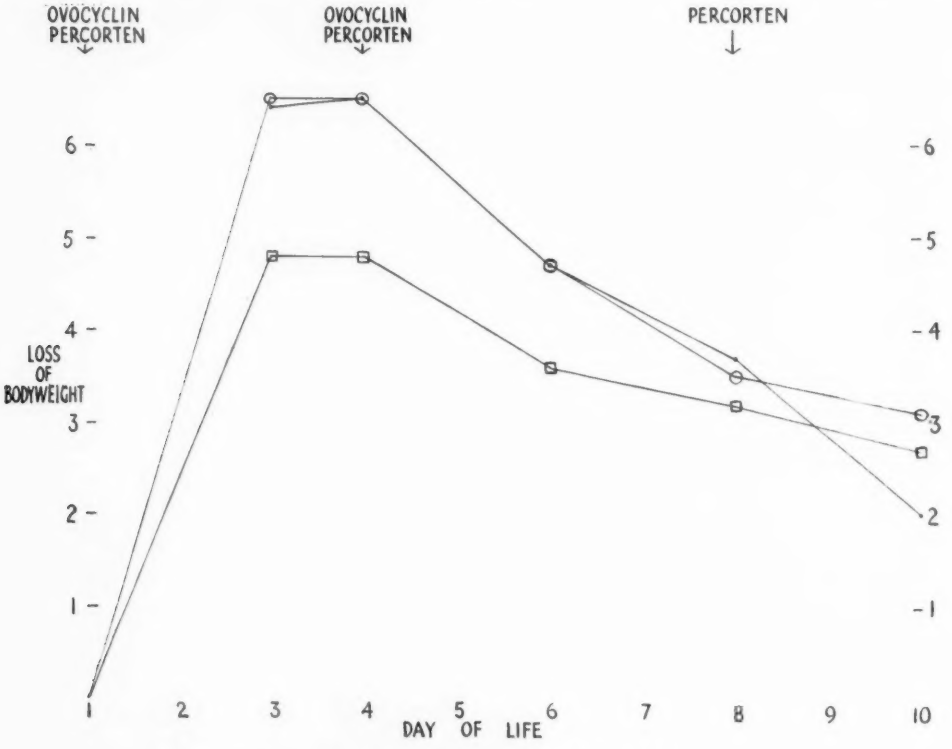

FIG. 3.—Percentage loss of birth weight
Dot, average for control group.
Circle, average for oestradiol group.
Square, average for Percorten group.

the control group of infants was seven pounds, for the one treated with oestradiol it was seven pounds three-and-a-half ounces, and for the one treated with desoxycorticosterone it was seven pounds ten ounces. From the results two facts are plain : first, the progress of the infants treated with the oestrogen is identical with that of the controls. Secondly, infants treated with Percorten show a maximum loss of weight amounting to 4·8 per cent. of their birth weight on the third day of life as compared with 6·5 per cent. in the other infants investigated. Such a difference is significant for Halpern (1934) could not reduce the loss of weight more than 1·14 per cent. This diminution was effected by the administration of an isotonic solution and adequate milk feeds to maintain the infant's weight from the day of birth.

Moncrieff (1936) emphasizes that the girl babies react better to oestrogens

than the boys. This is supported by table 2, in which the weight progress of both sexes treated with oestradiol is contrasted. This is probably due to the stimulating action of the endocrine upon the growth of the endometrium in the female. In an attempt to predict the weight progress from the degree of gastric acidity the weight chart of each infant was correlated with its gastric secretory response to test-meals throughout the first week of life. By this means it was impossible to forecast the amount of weight an infant would lose during the week, or the rate at which it would regain its birth weight. However, one interesting fact was noted on the seventh day : only eight infants belonging to either the control or oestrogen group had a total acidity of 20 c.c. or more, and they, on the average, had regained their birth weight on the seventh day of life. Infants treated with Percorten behaved in a similar manner. Eleven of this group had an acidity corresponding in degree to the former groups, and their weight was 1·9 per cent. less than their birth weight of the seventh day as compared with 4·4 per cent. for the remaining infants in the same group.

TABLE 2

NO. OF INFANTS	AVERAGE BIRTH WEIGHT	PERCENTAGE LOSS OF BIRTH WEIGHT				
		DAY 3	DAY 4	DAY 6	DAY 8	DAY 10
10 males ..	7 lb. 3 oz.	6·6	7·1	4·6	4·1	3·3
10 females ..	7 lb. 4 oz.	6·2	6·0	4·8	2·8	2·6

In concluding an account of the results it should be noted that all weights were recorded, but forty-seven of the gastric specimens were either unobtainable or contaminated with bile or blood.

Discussion

Two problems arise: first, why does the type of secretory response to a test-meal vary so markedly during the first week of life? And, secondly, has the reduction in the physiological loss of weight by means of Percorten any significance? In seeking the explanation of the former, it is necessary to recall the following factors which influence gastric secretion :

(1) Admixture of test-meal with the stomach contents, a factor which is constant throughout the investigation. The swallowing of saliva or regurgitation of intestinal contents may produce changes in the acidity of fasting juice.
(2) Variation in the parietal cell secretion itself, a factor considered of little importance at the present day.
(3) Peptic secretion ; this can be dismissed, as it plays such a minor part.
(4) Reabsorption of hydrochloric acid, which is considered by some authorities to be of importance.
(5) A specific diluting secretion or mucus may also be an important factor.

Buffer containing fluids, such as protein, phosphates and bicarbonates, will diminish acidity, and they are thought to be primarily responsible for observed variations in the gastric acidity in adults (Hollander, 1939).

Of all these factors, the only one likely to be responsible for the gross alterations in the gastric acidity during the first two or three days of life would be a defect in the mechanism of reabsorption of hydrochloric acid. If this is not accepted, another possible explanation is the presence of a gastrogenic substance in the infant's circulation, received in utero from the mother. At birth its concentration in the blood is similar to that in an adult or in the mother, but, as time passes the concentration falls, with a corresponding diminution in the gastric acidity (Miller, 1941).

Attention has been drawn to the maximum physiological loss of weight at birth. Normally it averages 6·5 per cent. of body weight (Hess, 1922) or 7·5 to 7·8 per cent. (Pfaundler, 1916; Pies, 1911) which is comparable with the figure of 6·4 to 6·5 per cent. for the control and oestradiol groups of infants under investigation. Babies treated with desoxycorticosterone show a striking difference in losing 4·5 per cent. of their birth weight. In the past, the weight loss was considered to result from a combination of factors : passage of 2½ to 6½ oz. meconium (Camerer, 1900 ; Hirsch, 1910); depletion of fluid via the skin, lungs, kidneys, and occasionally from the stomach; reduction of body tissue, as evidenced by wrinkling and lack of turgor of the skin; and, lastly, inadequate nourishment. Now, adreno-cortical insufficiency may be added to the above list. The blood biochemistry of the newborn supports the practical demonstration of the hormonic efficiency. In table 3 the rise in the protein and non-protein nitrogen during the first four days of life is apparent. Haemoconcentration beginning at birth is also associated with suprarenal insufficiency. The maximum concentration of the blood occurs six to seventy-two hours after birth as judged by the haematocrit (Bruch and McCune, 1936) and the erythrocyte count (Lippman, 1924). It is suggested that the cause of the above findings results from the involution of the gland or from traumatic shock at birth.

TABLE 3

DAY OF LIFE	PROTEIN (GM. PER CENT.)		NON-PROTEIN NITROGEN (MGM. PER CENT.)	
	MARPLES (1932)	BRUCH (1936)	LUCAS (1921)	BRUCH (1936)
1	5·9	6·61	42·2	35·0
2	6·07	6·26	46·3	40·6
3	6·23	6·78	36·3	32·0
4	7·07	7·32	—	—

Conclusion

There were no toxic reactions or vaginal bleeding produced by oestradiol-dipropionate or desoxycorticosterone acetate therapy. Nevertheless, massive doses as used in these investigations over a prolonged period may be dangerous. Robson (1940) states that oestrogenic substances can become carcinogenic in their action, and toxic effects upon the kidney have been observed by Korenchevsky (1940). The adreno-cortical hormone, on the other hand, can produce varying grades of oedema which, if not relieved, may terminate in congestive heart failure (Ferrebee et al., 1939).

The weight progress of the female infants may be aided by oestradiol and the maximum physiological loss of weight at birth diminished by desoxycorticosterone; neither of these facts, however, is sufficient to warrant the use of the hormones in normal babies, since the improved weight progress of girl babies is merely the result of a localized hormonic action upon the endometrium of the uterus, and the diminution in the initial loss of weight does not aid the ultimate weight progress.

The gastric acidity was not influenced by the hormone therapy. This is not altogether surprising, for both Atkinson (1939) and Sandweiss (1939) detected no difference in the acidity of stomach contents in man or dogs when they were treated with oestrin. The mother, however, is responsible for the gross variation in her infant's gastric acidity during the first few days of life. The infant's progress in weight is not influenced by the degree of acidity, but it was noted that infants thriving best at a week old had a gastric acidity of 20 c.c. N/10 HCl or more after a test-meal consisting of equal parts of milk and water.

The investigations were performed in the Simpson Maternity Pavilion, The Royal Infirmary, Edinburgh, by kind permission of Prof. R. W. Johnstone, Dr. W. F. T. Haultain, and Dr. Douglas Miller, who allowed the work to be carried out in their wards. The hormones were supplied by Ciba, Ltd., in the form of Ovocyclin-P and Percorten, for which I am grateful. Thanks are especially due to Prof. Charles MacNeil for his guidance and interest, and to Sister Taylor and nursing staff for their co-operation in collecting specimens and observations.

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A SURVEY OF PRIMARY INFANTILE AND JUVENILE PNEUMONIA *

BY

MOUNTJOY ELLIOTT, M.A., D.M., M.R.C.P.I.

Statistical review

The material for review was collected from the records of three Dublin Hospitals for the years 1937 to 1939. All patients dying within twenty-four hours of admission, or in whom signs of improvement had set in before starting treatment, were excluded. The cases were clinically divided into the two groups of lobar and atypical pneumonia. The former showed clinical evidence of lobar consolidation, the latter consolidation of an irregular patchy nature. Eight hundred and ninety-five cases were studied. Table 1 shows the age group distribution, and table 2 the combined fatality rates for the three years studied.

TABLE 1

	AGE (YEARS)	CASES
ATYPICAL PNEUMONIA	0–1	336
	1–2	160
	2–12	123
		619
LOBAR PNEUMONIA	0–1	59
	1–2	72
	2–12	145
		276

TABLE 2

CLINICAL TYPE	CASES	DIED	CASE-MORTALITY PER CENT.
All types	895	177	19·8
Atypical..	619	150	24·2
Lobar	276	27	9·8

The great importance of age in relation to death rate is well shown in table 3.

* Based on a Thesis for the degree of M.D., University of Dublin.

TABLE 3

AGE GROUP CASE-MORTALITY 1937 TO 1939

	MONTH GROUPS					YEAR GROUPS		
AGE	0–1	1–3	3–6	6–9	9–12	1–2	2–6	6–12
No. treated	19	61	88	97	130	232	182	86
Died	13	24	27	16	28	47	19	3
Mortality per cent.	68·4	39·3	30·6	16·5	21·5	20·2	10·4	3·5

The relationship of the clinical type of the disease to the death rate in Dublin is shown in table 4.

TABLE 4

AGE GROUP CASE-MORTALITY RATES FOR LOBAR AND ATYPICAL PNEUMONIA 1937–1939

LOBAR	MONTH GROUPS					YEAR GROUPS			TOTAL
AGE GROUP	0–1	1–3	3–6	6–9	9–12	1–2	2–6	6–12	
No. of cases.. ..	2	6	9	13	29	72	83	62	276
Deaths	2	2	4	2	2	8	6	1	27
Mortality per cent. ..	100	33·3	44·4	15·4	6·9	11·1	7·2	1·6	—
ATYPICAL AGE GROUP	0–1	1–3	3–6	6–9	9–12	1–2	2–6	6–12	
No. of cases.. ..	17	55	79	84	101	160	99	24	619
Deaths	11	23	22	26	22	33	13	0	150
Mortality per cent. ..	64·7	41·8	27·8	30·9	21·8	20·9	13·1	0	—

It will be noticed that clinical lobar pneumonia in infants of the 0–6 months age group is comparatively rare, but that when it does occur it tends to carry with it a death rate as high as that of atypical pneumonia; thereafter atypical pneumonia is about twice as fatal as lobar.

The importance of pneumonia as a social danger to the children of the Irish Free State is shown by reference to the official statistics published by the Eire Government. These show that in 1936 and 1937 of every 1,000 children born at full term in Eire, 8·96 and 8·34 respectively died of certified pneumonia under one year of age. The disease ranks third as the greatest slayer of full-time infants in Dublin in the first year of life.

Clinical evidence has now firmly established the value of chemotherapeutic treatment in the adult pneumonias, but little evidence has yet been collected of the value or otherwise of chemotherapy in treating the pneumonias of infants and young children.

Tables 5 and 6 were drawn up after careful study of the records of three Dublin hospitals.

TABLE 5

ANNUAL CASE-MORTALITY RATES FROM LOBAR AND ATYPICAL PNEUMONIA IN CHILDREN AGED 0–1 YEAR

LOBAR PNEUMONIA

	1937	1938	1939
Cases	8	32	19
Died	0	11	7
Mortality per cent.	0	34·4	36·8

ATYPICAL PNEUMONIA

	1937	1938	1939
Cases	74	134	118
Died	31	49	29
Mortality per cent.	41·9	36·6	24·6

TABLE 6

ANNUAL CASE-MORTALITY RATES FROM LOBAR AND ATYPICAL PNEUMONIA IN CHILDREN AGED 1–2 YEARS

LOBAR PNEUMONIA

	1937	1938	1939
Cases	16	37	19
Died	3	8	4
Mortality per cent.	18·47	21·6	21

ATYPICAL PNEUMONIA

	1937	1938	1939
Cases	24	80	56
Died	5	17	11
Mortality per cent.	20·8	21·3	19·6

The number of cases makes statistical deductions inconclusive, but there would appear to have been a tendency for the death rate from atypical pneumonia in the first year of life to be lowered, whilst the rates in lobar pneumonia for the first two years of life appear to have been unaffected. As these figures appeared unsatisfactory compared with the reported results from the newer methods of therapy in the adult pneumonias, an investigation of the results of individual methods of treatment in these three hospitals was undertaken (table 7).

TABLE 7

PERCENTAGE CASE-MORTALITY FOR VARIOUS METHODS OF TREATMENT, IN CHILDREN AGED 0–12 YEARS

TREATMENT	CASES	DIED	PERCENTAGE MORTALITY
Symptomatic	460	101	21·9
M and B 693	158	33	20·9
M and B 693+Serum	163	16	9·8
Serum	54	18	33·3
Sulphanilamide	12	5	41·7
Vaccine	48	12	25

Serum=Felton's anti-pneumococcal horse serum Types 1 and 2.
Vaccine=Compound pneumococcal, streptococcal and H. influenzae vaccine, prepared by Evan's Biological Institute.

From this table, it will be seen that the best results may be expected from the combined use of sulphapyridine with anti-pneumococcal serum, and that in the very young, chemotherapeutic measures alone may not offer the best chances of recovery. This point depends largely on two factors, viz. differences in immunity factors in children, and differences in the anatomico-pathological type of disease in young children.

Immunity factors in children

The principal antibody mechanisms involved in pneumococcal infections are agglutination and precipitation. Complete dissolution of the organisms is impossible without additional phagocytic activity, but there is no evidence to show that such activity is lacking in infants.

Fleming (Fleming, 1938; Maclean, Rogers and Fleming, 1939) has shown that the addition of a specific antibacterial serum to a mixture of blood and M and B 693 increases its antibacterial action to pneumococci, and has further substantiated these findings by experiments in mice and rabbits (1939). The function of the specific antiserum is the neutralization of the specific soluble substance, which is the toxic substance proper of the pneumococcal capsule. This neutralization occurs in the circulation and peripheral organs (Kempf and Nungester, 1939), and apparently follows a mathematical ratio. The following experiment was carried out in order to determine whether the very young produce such antibacterial substances or not.

Technique. A slide agglutination technique, described by Bullowa (1937), was used. A drop of the patient's serum was mixed with a drop of the specific antigen consisting of killed suspensions of pneumococci, two billions per c.c. on glass slides. Antigens of types 1, 2, 3, 4, 5, 6, 7, 8 and 14 pneumococci were used. Slides were air cooled and fixed in a solution of 94 c.c. water, 1 c.c. glacial acetic acid, 5 c.c. formalin (40 per cent. formaldehyde). When dried they were stained for a few seconds with Loffler's alkaline methylene blue stain, dried and examined by 1/12 oil immersion lens. Control slides were also put up consisting of (i) saline or normal blood with antigen; (ii) antigen with type specific serum of known agglutination titre. The agglutination is symbolically expressed as one of four degrees : −, ∓, ±, +.

A special polyvalent pneumococcal vaccine containing all the thirty-two types of pneumococci with several strains of certain types, was given by subcutaneous injection to healthy subjects of various ages, and their sera were examined by the above technique on the third and seventh days following inoculation. Injections were given on three successive days as follows: 0·1 c.c. 0·2 c.c. and 0·4 c.c. The vaccine contained 100 million organisms per 0·1 c.c., and was prepared by Professor Alexander Fleming in the Inoculation Department of St. Mary's Hospital, London.

Results. Table 8 shows the results in six subjects aged eight weeks to fourteen years.

TABLE 8

THIRD DAY TITRATION

ANTIGEN TYPE	SUBJECTS						ANTIGEN SPECIFIC AGGLUTINATING SERA	ANTIGEN SALINE
	1	2	3	4	5	6		
1	−	−	−	−	−	−	+	−
2	−	∓	∓	−	−	∓	+	−
3	∓	∓	−	−	−	−	+	−
4	∓	−	±	−	∓	−	+	−
5	±	−	−	∓	−	±	+	−
6	±	−	±	−	−	−	+	−
7	−	−	−	−	−	−	+	−
8	−	−	±	∓	−	−	+	−
14	−	−	−	−	−	−	+	−

SEVENTH DAY TITRATION

ANTIGEN TYPE	SUBJECTS						ANTIGEN SPECIFIC AGGLUTINATING SERA	ANTIGEN SALINE
	1	2	3	4	5	6		
1	−	−	−	−	−	−	+	−
2	−	∓	∓	−	−	−	+	−
3	∓	±	−	±	−	−	+	−
4	∓	−	±	−	∓	−	+	−
5	±	−	−	∓	−	+	+	−
6	±	−	∓	−	−	−	+	−
7	−	−	−	−	−	−	+	−
8	−	−	∓	±	−	−	+	−
14	−	∓	∓	−	−	−	+	−

Patient 1 .. .. .. Age 5 years.
„ 2 .. .. .. „ 8 „
„ 3 .. .. .. „ 14 „
„ 4 .. .. .. „ 3 „
„ 5 .. .. .. „ 8 weeks.
„ 6 .. .. .. „ 2 years.

Table 9 shows the results of six subjects aged six years to sixty-eight years using doses of 0·2, 0·5 and 1·0 c.c. respectively at the same time intervals.

TABLE 9

THIRD DAY TITRATION

ANTIGEN TYPE	SUBJECTS						ANTIGEN SPECIFIC AGGLUTINATING SERA	ANTIGEN SALINE
	1	2	3	4	5	6		
1	−	−	−	−	−	−	+	−
2	−	−	−	−	−	−	+	−
3	−	−	−	∓	±	∓	+	−
4	∓	−	−	−	−	−	+	−
5	∓	−	−	−	−	−	+	−
6	−	−	−	−	−	−	+	−
7	−	−	−	−	−	−	+	−
8	±	−	+	−	−	−	+	−
14	−	−	−	−	−	−	+	−

No. 2 was a patient suffering from a Lederer's anaemia.

SEVENTH DAY TITRATION

ANTIGEN TYPE	SUBJECTS						ANTIGEN SPECIFIC AGGLUTINATING SERA	ANTIGEN SALINE
	1	2	3	4	5	6		
1	−	−	−	−	∓	−	+	−
2	∓	−	−	−	−	−	+	−
3	±	∓	−	−	±	±	+	−
4	∓	∓	−	∓	∓	∓	+	−
5	∓	−	±	∓	+	−	+	−
6	∓	−	−	−	−	−	+	−
7	−	−	−	−	−	∓	+	−
8	±	∓	+	∓	±	∓	+	−
14	∓	−	−	−	∓	∓	±	−

+ titres ranged according to type from 1/5 to 1/60.

Patient 1 .. .. .. Age 56 years.
,, 2 .. .. .. ,, 39 ,,
,, 3 .. .. .. ,, 4 ,,
,, 4 .. .. .. ,, 68 ,,
,, 5 .. .. .. ,, 12 ,,
,, 6 .. .. .. ,, 6 ,,

These experiments tend to show that the anti-pneumococcal antibody-producing mechanism of very young children is incapable of producing the necessary immunological substances necessary to complete the destructive powers offered by chemotherapy alone. In adults, sensitizing doses of pneumococci inhaled from time to time have given to the antibody mechanism the potential energy necessary to bring it rapidly into action when pathogen-producing organisms gain entry into the tissues. Sulphapyridine in adults often kills the pneumococci so rapidly and effectively that the stimulus to antibody production is eliminated. This may explain the delayed resolution so often seen in such cases. It is important to maintain therapeutic levels of the

drug in the blood stream for seven to ten days. There is evidence to show that in adults sulphathiazole (Kneeland and Mulliken, 1940) may prove a better drug because, being less rapidly bactericidal, there is more opportunity for the immunity mechanism to come into action. This should tend to prevent acute relapse and perhaps delayed resolution. This brings out the important point that the assessment of treatment in the pneumonias of children should be considered strictly from the age group point of view. Once a child passes the age of two years it enters, immunologically speaking, the realm of the adult pneumonias. The reason for this is not only a change in the mode of the immunity response, but also a change in the anatomico-pathological type of the disease. Table 10 taken from Reimann's book on the pneumonias (1938) shows this clearly.

TABLE 10

RELATIVE INCIDENCE OF LOBAR AND ATYPICAL PNEUMONIA IN CHILDREN

(From various authors)

	IN ALL CHILDREN		CHILDREN UNDER TWO		CHILDREN OVER TWO	
	NUMBER OF CASES	PER-CENTAGE	NUMBER OF CASES	PER-CENTAGE	NUMBER OF CASES	PER-CENTAGE
Lobar	1,144	76	437	60	707	92
Atypical	362	24	300	40	62	8

The same author points out that lobar pneumonia has a surprisingly low death rate in later childhood but is considerably more dangerous in infants. Pneumococcal pneumonia in general is about three times as fatal in children less than two years of age as in older ones.

In view of these findings the present position of pneumonia occurring in this all-important age group of 0–2 years of age may be considered. Eighty-two per cent. of the 106 cases dying from pneumonia in these three hospitals in 1937 and 1938, and sixty per cent. of the forty cases dying in 1939, were in children under one year of age. Has there been a bettering of the lot of these very young patients in recent years? A glance at table 11, prepared from the records of the three hospitals, shows that the answer is both yes and no. There has been an actual increase in the fatality rates from lobar pneumonia whilst there has been a steady fall in the death rates from the atypical forms.

Methods of therapy in infantile pneumonia

The chief reasons for the apparent failure of the newer therapy in infantile pneumonia is that too much reliance is placed on chemotherapy alone, and that no effort is made to better the developing immunity mechanisms by the giving of serum. To establish this point the results of various treatments in a

TABLE 11

ANNUAL MORTALITY RATES FROM PNEUMONIA IN CHILDREN AGED 0–2 YEARS

	1937			1938			1939		
	CASES	DIED	MORTALITY PER CENT.	CASES	DIED	MORTALITY PER CENT.	CASES	DIED	MORTALITY PER CENT.
Lobar ..	24	3	12·5	69	19	27·2	38	11	28·9
Atypical	98	36	36·7	214	66	30·8	174	40	22·9

series of very young children must be carefully studied. Serum is indeed expensive (approximately £10 to £20 worth are necessary for treating a severe case of pneumonia in an adult) but as Reimann economically puts it, ' When one compares its cost with the cost of an operation for appendicitis, the mortality of which is far less than that from pneumonia, the price is indeed not excessive. Furthermore, the shortening of the duration of the pneumonia and reduction in the number of days spent in hospital and in expense of nursing, result in savings which often overbalance the cost of serum.' All children with pneumonia who are under two years of age should be admitted to a properly equipped hospital as soon as the diagnosis is made. There are three reasons for this : Firstly, the giving of serum intravenously to infants requires considerable skill. Secondly, there is now substantial evidence that small blood transfusions help these patients over a severe infection; and thirdly, the danger of sudden dehydration with its devastating after effects requires careful watching and immediate counteraction by the administration of parenteral fluids. Cyanosis may necessitate the use of an oxygen tent. In a large city, a special team could be got together as an independent unit of a hospital for dealing with all cases of infantile pneumonia.

Dr. F. C. McDonald of the Boston Floating Hospital has shown (1939) what excellent results may be obtained by good symptomatic treatment and skilled nursing. His method is to give oxygen and sedatives liberally and to ensure an adequate intake of food, fluids, glucose and vitamin concentrates (A, B, C and D). Except when breathing is made difficult by tenacious sputum, a pleural effusion or pharyngeal complications, he gives morphine freely, his dosage being 1/24 grain at 15 lb., 1/12 grain at 30 lb. and 1/6 grain at 75 lb. The use of morphine in this way requires great judgment.

Special considerations. Since sulphapyridine is insoluble in relatively neutral solutions, its absorption from the gut is likely to be influenced by the changes in pH which fluids may undergo in the small intestine, and by the varying rapidity with which fluids may pass along the gut in health and disease. If diarrhoea or vomiting is present there will not only be a loss of sulphapyridine from the bowel or stomach but the actual amount of fluid in the bowel may be so reduced as to render the solution of an adequate therapeutic amount of the drug impossible. Again, if the bacterial flora of the bowel is such as to reduce

the pH of its contents, solubility of sulphapyridine may also be reduced. Thus, apart from combating dehydration and acidosis, the parenteral administration of glucose-saline with sodium sulphapyridine has an important rôle in therapy. In such an acute disease as pneumonia it may be advisable in severe cases to control the level of blood sulphapyridine by chemical estimation. The method described by Werner (1939) is an admirable one for clinical purposes. Using this method, I found that adequate blood levels of the drug could be maintained in the average case by giving the following dosage:

AGE	DOSAGE OF M AND B 693
0–3 months	¼ tablet every 4 hours.
3–6 months	½ tablet every 6 hours.
6 months–1 year	½ tablet every 4 hours.
1–2 years	1 tablet three times a day.

These findings closely agree with the dosage worked out by Hynes (1940) at the Hospital for Sick Children, Great Ormond Street.

In poorly nourished and maldeveloped children, a severe acute secondary anaemia is liable to occur, especially in the presence of septicaemia or when chemotherapy is given over a prolonged period. Such anaemia reduces considerably the immunity response. Early blood transfusion is often a life-saving procedure in such cases. The general response of the child to treatment should be the main guiding factor for its use, since haemoglobin estimations are often misleading owing to the variation of blood-concentration which occurs in severely sick children.

The use of type specific serum is important. Curnen (1939), at a meeting of the Massachusetts Medical Society, gave a report on thirty-four cases of type XIV pneumonia in children of whom twenty-two were under two years of age, treated with type specific serum alone. All survived, and all but three with complications or a mixed infection responded promptly to adequate doses of the serum. Bullowa had an 8·5 per cent. mortality in 330 cases between 1934 and 1937.

Don et al., 1940 have shown that the best results in adults with pneumococcal septicaemia are obtained by the use of specific serum combined with chemotherapy. There is a 100 per cent. mortality amongst untreated cases of pneumococcal septicaemia in children under two years of age. The necessity of combined therapy is therefore most urgent in young children with pneumococcal septicaemia.

Special mention should be made of pneumonia occurring in malnourished, underdeveloped or premature infants. Modern methods of treatment have given these a better chance of recovery, but the necessity of maintaining nutrition whilst the struggle is in progress is still of vital importance. Breast feeding should be continued if practicable, but if this is impossible, fresh or stored breast-milk from a healthy donor, preferably the mother, should be obtained.

Non-pneumococcal pneumonias

Poor laboratory technique may fail to show the presence of other primary or secondary pathogenic organisms. In children under twelve years of age

60 to 70 per cent. of non-pneumococcal pneumonias are due to streptococci and about 6 per cent. to staphylococci. B. Friedlander pneumonia in young children is practically unknown. If after forty-eight hours of combined sero-chemotherapy, there has been no clinical amelioration of the symptoms, further bacteriological evidence must be sought to confirm the nature of the pathogen responsible. It is in such cases that lung suction is of great value. Bullowa in four years did 405 lung suctions in children, and 122 cases gave a growth. Pneumothorax was the only complication. If streptococci appear responsible, the use of sulphanilamide should be considered. No mention will be made of the acute tuberculous pneumonias or any of the rarer acute primary pneumonias of children.

Prognosis

The four most important factors in determining prognosis are: (i) the age of the child, (ii) the time of starting treatment, (iii) the general condition of the child at the onset of the pneumonia, and (iv) the treatment given.

The chances of recovery in children over the age of two years, are as good as those of a young adult. If the child is under two years of age difficulties and failures are likely to be encountered. If specific treatment is delayed, the prognosis will follow the lines of a case of perforated peptic ulcer, in which the passing of every hour without treatment brings the patient nearer to death. Poorly developed, undernourished and premature children have the worst prognosis.

Summary

A review of 895 cases of juvenile pneumonia in Dublin for the years 1937 to 1939 is given. The age of the patient and the pathological type of causative organism are still of great importance in determining prognosis. There appears to have been a lowering of the death rate from atypical pneumonia in the first year of life since the introduction of chemotherapy, but the results in treating lobar pneumonia by chemotherapy alone in infants are disappointing. Statistical and experimental studies suggest that the administration of serum with chemotherapy in the infantile pneumonias gives the best results. Experiments indicate that the anti-pneumococcal immunity mechanism is relatively weak in infants. Children over two years of age with pneumonia can be treated in a similar manner to adults. All infants under two years of age with pneumonia should be treated in a properly equipped hospital. Blood transfusion, parenteral fluids, oxygen, sedatives and skilled nursing are almost as valuable as chemotherapy in severe cases of pneumonia in infants. They are particularly important in premature and poorly nourished children. The importance of maintaining weight during treatment is emphasized; efforts to continue breast feeding should be made. Prognostic factors are discussed.

Thanks are due to the medical staffs of Harcourt Street and Temple Street Children's Hospitals and Cork Street Fever Hospital for access to their records, and to members of the staff of the National Children's Hospital, Harcourt

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MALIGNANT HYPERTENSION IN CHILDHOOD

BY

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Essential hypertension remains one of the most important problems in clinical medicine. Until the cause is discovered both nomenclature and classification must of necessity be provisional and incomplete. Nevertheless in recent years, increasing attention has been given to this subject and certain definite advances made. This applies particularly to the so-called malignant type of primary or essential hypertension. Malignant hypertension may be defined as a progressive, generalized, vascular disorder associated with gross hypertension, in which renal dysfunction is a secondary and late manifestation. The condition is predominantly one of middle life and in consequence its occurrence in childhood has received little notice. For this reason the following case has been presented in some detail. A careful study of the literature of the last twelve years has revealed only eleven cases below the age of fourteen which fulfil the clinical criteria and of these only four were confirmed at autopsy.

In this article it is proposed to indicate the essential features of the condition in childhood as far as this is revealed by the eleven cases previously mentioned, and to describe in detail a case under my own care.

The main features are shown as follows:—

TOTAL CASES	12
AVERAGE AGE	10 years.
SEX—	
Male	4
Female	8
CLINICAL FEATURES—	
Headache	12
Vomiting	12
Papilloedema	12
Visual disturbance	8
Haemorrhage	7
Convulsions	6
Abdominal pain	2
Exertion dyspnoea	1

These symptoms and signs are associated with a severe and progressive hypertension for which no cause can be found. In the above cases the average highest systolic pressure recorded was 230 mm. of mercury and the diastolic

160 mm. The course of the disease is rapid and relentless. The average duration in this series was two years. The longest period of survival after the onset of symptoms was five years and the shortest six months.

Haemorrhage may take the form of haematuria, melaena or epistaxis. In five cases intermittent but severe haematuria was an outstanding feature. Renal failure is a terminal event and the blood urea rarely rises to high levels. Papilloedema is always present. The striking features are the severity of the hypertension, the rapid tempo of the course and the fatal ending. Death occurs from cardiac, cerebral or renal defect or from intercurrent infection.

The adult picture has been clearly described by Wagener and Keith (1939) in America and by Ellis (1938) in this country. The adult and childhood pictures are similar. There are, however, certain differences. The haemorrhagic features, notably haematuria, so striking in some of the children, are less marked in adults; but nervousness, lack of energy, dyspnoea on exertion and nocturnal frequency of micturition, infrequent in childhood, are prominent adult symptoms. In both, the onset may be sudden or insidious; in both, a rapid course leads inevitably to a fatal termination.

Pathology. It must be stressed that this is a generalized disease of the arterial system. In consequence, the characteristic lesions are found not only in the kidney but also in the bowel, brain, pancreas, adrenals, testes and elsewhere. In America, biopsy of the vessels of the pectoral muscles is part of the routine examination in suspected cases.

MORBID ANATOMY. The predominant changes are found in the heart and kidneys. There is marked left ventricular hypertrophy. The kidneys as a rule are only slightly reduced in size, though in certain cases one has been smaller than the other. The histology of each kidney in such cases was similar, and there was nothing to suggest congenital abnormality. The surface shows diffuse, flat granular elevations of varying size, standing out above slightly depressed red areas. Petechial haemorrhages may or may not be present. The granularity referred to is not marked and the capsule strips fairly easily. On section the cortex and medulla are sharply demarcated for the most part, though the cortical markings may be obscured by greyish flecks and streaks. The renal pelvis frequently shows dark red haemorrhagic areas and the renal artery may be thickened.

HISTOLOGY. The lesions are more distinctive and two well-defined processes are evident. The smaller arteries show a cellular proliferation of the intima often leading to occlusion of the lumen. This is called by Ellis ' endarteritis fibrosa ' and is clearly distinguished from the arterial thickening associated with the increase in elastic tissue present in all cases of hypertension. The arteriolar lesions are more severe in character. The walls of the arterioles are swollen by the presence of a homogeneous material which appears purplish in colour when stained with haematoxylin and eosin. This change has been termed ' acute fibrinoid ' necrosis. It may be followed by occlusion of the lumen, infiltration of the vessel wall with blood, or local aneurysm formation.

In the kidney itself these lesions are well developed. Fibrinoid necrosis of the individual capillary loops or of the whole glomerulus may be seen. This

may lead to adhesion of capsule and tuft. Proliferative capsulitis is sometimes present, but true crescent formation is rare. The interlobular arteries show endarteritis fibrosa and the smaller arterioles, particularly the afferent arterioles to the glomeruli, show fibrinoid necrosis. In the arcuate and larger arteries elastic lamination may be present. The tubules may show hyaline droplet degeneration and there is some increase in the stroma with round-celled infiltration. Nevertheless, in spite of the widespread vascular damage, one of the striking features is the relative normality of the nephrons. In fact the majority of the glomeruli appear normal, in marked contrast to the picture of chronic glomerulo-nephritis.

The vascular changes described in detail for the kidney, are found in other organs, notably in the pancreas, adrenals, bowel, brain and retina. The whole picture is in fact one of diffuse arterial and arteriolar disease.

Case report

J. O. D., female aged ten years was admitted to the Westminster Hospital on August 7, 1938. The child had complained of vague headaches for three to four years. Two years before admission these became severe, frontal in position and associated with vomiting. For the preceding six months she had experienced intermittent gross haematuria and failing vision.

Measles and chicken pox had occurred in early childhood but there was no history of acute nephritis or recurrent tonsillitis.

Examination. This revealed a thin sallow child with no obvious oedema. The tonsils appeared healthy though the tonsillar glands were palpable.

CARDIO-VASCULAR SYSTEM. Obvious cardiac enlargement was present, associated with the classical signs of patent ductus arteriosus.

The blood pressure was 240/145 mm. Hg in the upper limbs and 270/160 mm. Hg in the lower.

EYES. Both retinae showed extensive changes, with papilloedema, exudate and haemorrhages. Vision: right, 6/60; left: patient was just able to count fingers at three feet.

URINE. At first macroscopic haematuria was present but this soon cleared. In the interval there was only a trace of albumin, a few red cells and no casts. The urine was sterile.

BLOOD UREA (8.8.38) 43 mgm. per cent. Urea clearance 40 per cent. of normal.

BLOOD PICTURE (8.8.38): Red blood cells 4,600,000. Haemoglobin 82 per cent. (23.8.38) Red blood cells 3,600,000. Haemoglobin 56 per cent.

Progress. For ten days haematuria continued and there was a sharp bout of epistaxis. After this, her general condition improved and she gained 4 lb. in weight. In view of the political situation she was removed to a provincial hospital on September 9, 1938.

On October 17, 1938 she was re-admitted to the Westminster Hospital. The blood pressure in the arms was now 250/150 mm. Hg, and retinopathy more extensive. A further severe attack of haematuria occurred soon after admission. The blood urea was now 61 mgm. per cent. A lumbar puncture revealed an increase in pressure to 275 mm. of cerebro-spinal fluid, but an otherwise normal fluid. The child's condition now began to deteriorate rapidly. Haematuria continued until November 9, 1938. Skiagraphs of the renal tract revealed no abnormality. For the ten days before death, the child became drowsy and presented severe abdominal pain with melaena. Pulmonary

oedema became evident and the blood pressure began to fall. At this stage drowsiness and high temperature with multiple arthritis, suggested a terminal septicaemia. Death occurred on November 14, 1938, two-and-a-half years from the onset of definite symptoms.

Autopsy. The body was wasted.

CARDIO-VASCULAR SYSTEM. The ductus arteriosus was patent and there was gross hypertrophy of the left ventricle. The smaller vessels throughout the body appeared firmer and more prominent than normal.

KIDNEYS. The right was normal in size and weighed 75 grammes. The left one was a little smaller. The capsule showed a reddish-yellow mottling with certain shallow depressions but no granularity. The cortico-medullary ratio was slightly diminished and the pattern a little distorted. There were numerous red blotches in both renal pelves and, on the right side, a haemorrhagic mass the size of a walnut projected into the lumen. The histology of this revealed endarteritis fibrosa and arteriolar necrosis of the pelvic vessels.

INTESTINES. There was a peritoneal exudate covering the last six feet of ileum. The bowel was purplish red in colour and incision revealed extensive haemorrhagic ulceration of the whole of the ileum and a large part of the jejunum. Apart from a few small angiomata in the liver, other organs appeared healthy.

Histology. The characteristic vascular findings, namely endarteritis fibrosa and acute arteriolar necrosis, were present in the kidney, renal pelvis, bowel. spleen, pancreas and adrenals. These are well illustrated in the accompanying plates (fig. 1 to 6).

It will be seen that this child presented the criteria of malignant hypertension, viz. headaches, vomiting, papilloedema, haemorrhage and a progressive hypertension with terminal renal dysfunction. There is one disappointing feature: the child was seen at a provincial hospital in 1935 as a case of congenital morbus cordis, but no record of the blood pressure at the time is available, When first seen by me she was entering the phase of renal failure. Nevertheless, in spite of severe hypertension and extensive bilateral retinopathy, the blood urea was only just above the upper limit of normal and subsequent renal histology revealed no evidence of a previous inflammatory lesion. A similar haemorrhagic enteritis has been recorded in one of the four children in whom autopsy was carried out (Klemperer and Otani, 1931).

Differential diagnosis. In a condition in which the ultimate etiology is still uncertain, differential diagnosis is clearly an important issue. The question arises as to whether this condition is a distinct entity or a clinical and pathological syndrome common to several disease processes. In answer to this, three conditions merit attention. The first of these is glomerular nephritis. No one will deny that in the terminal stages of this disease, vascular failure may rapidly occur, hypertension and retinopathy become intense and the picture resemble the terminal stage of malignant hypertension. In fact, when renal failure has supervened, a clinical differentiation may be impossible. A clear history of acute or sub-acute nephritis would, of course, suggest the answer. Histological examination would, however, be more conclusive. In chronic glomerular nephritis, although endarteritis fibrosa and arteriolar necrosis may be present in certain areas, their presence in organs other than the kidney is rare, whereas glomerular fibrosis, minimal in hypertension, would be everywhere visible.

The second condition, chronic pyelo-nephritis, has only recently received the attention it deserves. Weiss and Parker (1939) believe that this accounts

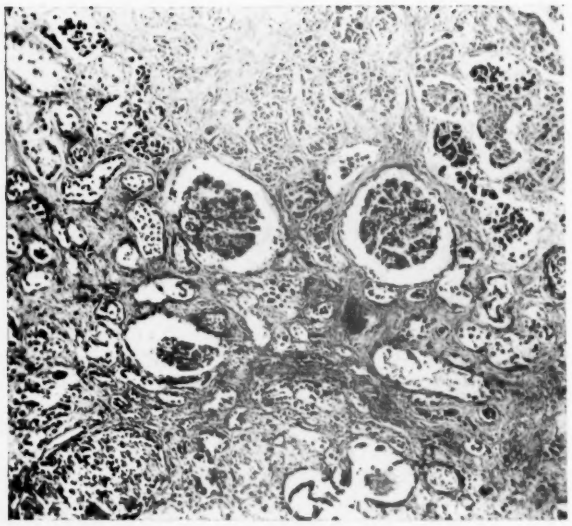

FIG. 1.—Renal parenchyma, showing almost normal architecture.

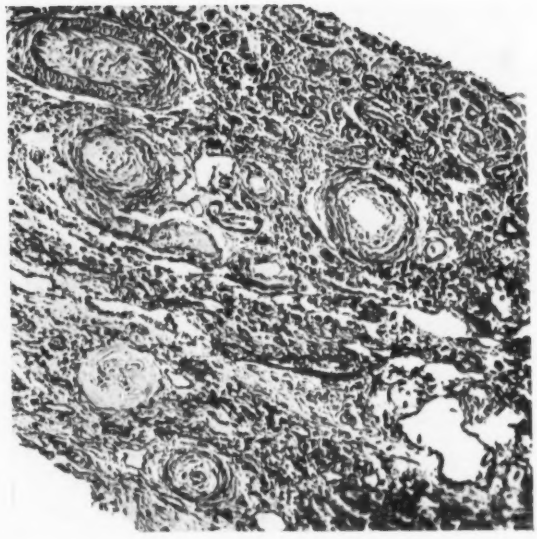

FIG. 2.—Kidney: vessels showing typical changes.

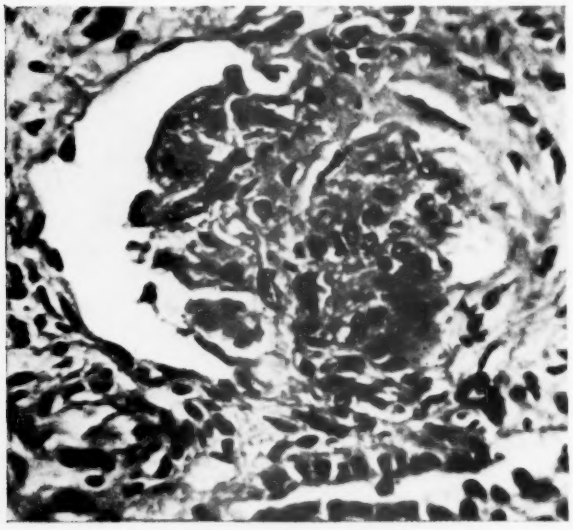

FIG. 3.—Glomerulus, showing areas of acute fibrinoid necrosis.

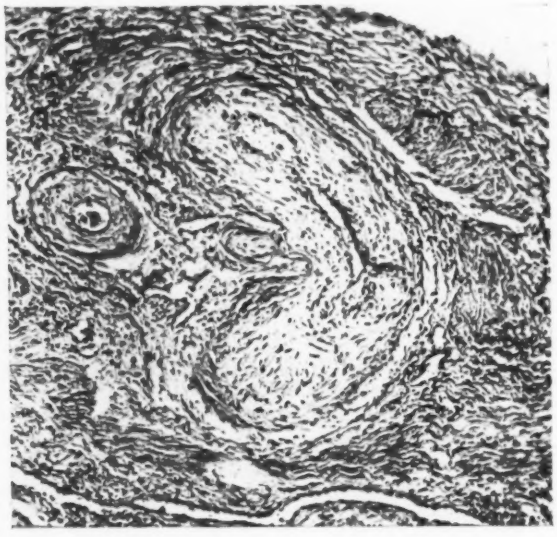

FIG. 4.—Mass in renal pelvis with vessel showing well-marked endarteritis fibrosa.

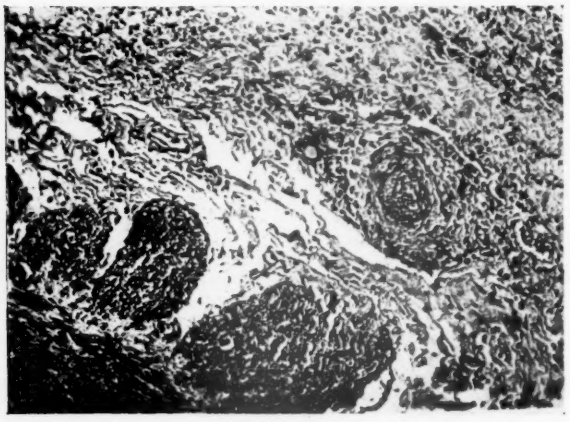

FIG. 5.—Vessels show aneurysm formation and rupture: small intestine.

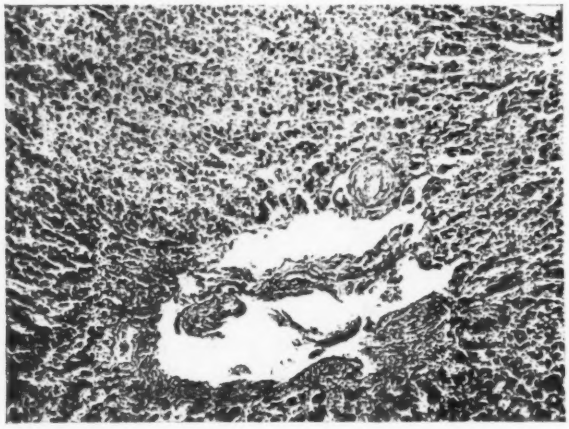

FIG. 6.—Endarteritis fibrosa in suprarenal vessels.

for 20 per cent. of all cases labelled malignant hypertension. They consider that pyelitis of early childhood can no longer be considered a benign and innocent infection of the renal pelvis. In a series of such cases followed for long periods, they found that some enter a latent or chronic phase and were later related to certain types of pregnancy toxaemia, subsequent attacks of pyuria and to arterial hypertension of progressive severity. They found vascular changes of the type seen in malignant hypertension in a baby of six months and a girl of twelve years, both of whom had had previous acute pyelo-nephritis.

Without describing healed or chronic pyelo-nephritis in detail, it is sufficient to say that, according to Weiss and Parker (1939), the full clinical picture of malignant hypertension may result. Nevertheless the histological features show unmistakeable differences; here again arteriolar necrosis may be present in the kidney, but in addition the tubules in certain areas are lined with flattened atrophic epithelium and filled with colloid casts; the glomeruli show peri-capsular fibrosis; there is marked infiltration of the interstitial tissue with inflammatory cells; the renal pelvis shows chronic inflammatory thickening together with thickening and infiltration of the renal capsule. Vascular changes in other organs are minimal or absent.

The third group is less well defined. It includes cases with the title of ' renal dysbiotrophy.' The causal factor here is presumed to be an underlying tissue inferiority. The kidneys are said to be small, pale and fibrosed and one may be much smaller than the other. Many of the glomeruli are atrophied or fibrosed, while others show varying degrees of chronic inflammatory reaction. Other developmental anomalies are not uncommon. The presence of a patent ductus arteriosus, in the case under consideration, and the difference in size of the two kidneys, might at first sight suggest that it belongs to this group, but the histology of both kidneys was identical and in no way comparable with that described above.

In addition to renal dysbiotrophy, this group includes cases of renal agenesis and renal hypoplasia, associated with hypertension. The picture is by no means clear; some may be undoubted cases of imperfect renal development but others previously included in this category are more probably examples of latent or chronic pyelo-nephritis.

It is clear from these facts that the clinical picture of malignant hypertension may be produced by more familiar disease processes. At the same time, a study of the histology suggests that there is a group of cases fulfilling all the essential criteria described in the earlier part of this paper. Whether this is in fact a disease entity, or is capable of further subdivision, remains to be seen. In diagnosing any suspected case of malignant hypertension during life there are therefore four conditions to be considered—a developmental renal anomaly, the terminal phases of chronic glomerular nephritis, chronic pyelo-nephritis, and primary malignant hypertension. The final diagnosis must await full histological investigation. Some idea of the relative distribution of these causes is given by Weiss and Parker (1939) in their assessment of fifty-five patients with ' contracted kidneys'; twenty-seven were due to nephrosclerosis of the benign or malignant types, eighteen to pyelo-nephritis and ten to glomerulo-nephritis.

Prognosis and treatment. The condition is invariably fatal. The maximum duration both for children and adults was five years and the minimum six months. The most important prognostic feature is the state of renal function. Once this begins to fail and especially when the blood urea rises, the end is not far distant. In such circumstances, treatment is essentially palliative. Surgical measures have certainly passed beyond the experimental stage, but at present their satisfactory application is confined to the more benign grades of hypertension. Wagener and Keith (1939) state that malignant hypertension does not respond satisfactorily to surgical treatment. The palliatives available are well known and need not be considered in detail. They include a daily regime with rather more rest than usual; sedatives, of which, in children, chloral hydrate in small repeated doses is probably the best; and measures for dealing with hypertensive attacks such as hypertonic salines per rectum or by the intravenous route ; venesection and lumbar puncture. Venesection would of course depend on the blood picture, but a severe degree of anaemia in this condition is rare.

The mechanism. The ultimate cause or causes of this type of hypertension await discovery. Promising investigation is still in progress and Wagener and Keith (1939) have recently reviewed with great clarity the march of events from the pioneer work of Gull and Sutton to the present day. This leaves the conception of malignant hypertension as a primary spastic, and initially reversible, vascular obstruction, leading ultimately to an organic and irreversible obstruction. In other words the vascular lesions which have been accepted as the criteria of the condition, are secondary and in the nature of a reaction to strain. Whether the disease runs a truly malignant course or takes a less rapid one, would seem to depend on the extent and persistence of the angiospasm and, to a certain extent, on the adaptability of the individual vascular system concerned. The main problem at the moment is the source and nature of the initial spastic agent. Upon this point finality has not yet been reached but the work of Pickering (1938), Goldblatt (1938), Wilson and Byrom (1939) and others, point strongly to a humoral rather than a nervous mechanism.

Summary

(1) The clinical and pathological picture of malignant hypertension in childhood, as described in recorded cases, is reviewed.

(2) A full description is given of the condition occurring in a child of ten years.

(3) Present views concerning pathogenesis are considered.

Thanks are due to Dr. Donald Paterson for permission to publish this case, to Professor Arthur Ellis for his confirmation of the histology and to Mr. Bridger for the photography.

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CASE REPORT

COMBINED FORMS OF MENINGITIS:

MIXED INFECTION OF THE MENINGES BY THE TUBERCLE BACILLUS AND MENINGOCOCCUS

BY

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It is rare to find two different causative organisms in a case of meningitis and of extreme rarity when one of these organisms is the tubercle bacillus.

Neal (1924) reported her analysis of 1535 cases of meningitis, in which only six (0·32 per cent.) were due to mixed organisms. All six cases were in children and included such organisms as the meningococcus, staphylococcus, b. paratyphosus B., haemolytic and non-haemolytic streptococcus, pneumococcus, and organisms of the b. coli group, but not the tubercle bacillus. An interesting case of mixed meningitis was described by Ravitch and Washington (1937) in a child whose blood culture grew meningococci and salmonella suipestifer. Both organisms were also cultured from the cerebrospinal fluid, but it was believed that the salmonella suipestifer had been introduced by blood contamination of the cerebrospinal fluid during lumbar puncture. Ashmun (1933) had five cases of mixed meningitis with pneumococci and streptococci present in the cerebrospinal fluid of all cases. In two cases the diplococcus catarrhalis was also present.

The source of the infection was significant in a case reported by Knights (1937). A boy was admitted to hospital with meningococcal meningitis and had a relapse in three weeks. Both haemolytic streptococci and meningococci were cultured from the cerebrospinal fluid and from his throat. Many cases are of otitic origin, and such a case was described by Huenekens and Stoesser (1927) in a child who had both haemolytic streptococci and pneumococci in the cerebrospinal fluid and who recovered after a bilateral mastoidectomy. The case of a baby whose cerebrospinal fluid grew on culture both pneumococci and bacillus influenzae was reported by Gaffney (1940), and an account of successful chemotherapy of haemolytic streptococcal meningitis and pneumococcal meningitis in the same patient is given by Reid (1940). but here the infections did not occur simultaneously.

The only reported case I could find of the tubercle bacillus being present with other organisms affecting the meninges was that of Moritz (1936). This patient died after both the tubercle bacillus and Friedlander's bacillus had been found in the cerebrospinal fluid. Griffith (1937) has described the case of a girl with tuberculous meningitis in which the organisms were mixed bovine and human tubercle bacilli, and refers to several similar cases.

Case report

The patient was a female child aged fourteen months, weighing 19 lb. 4 oz. She was a full-time baby, born by normal delivery, and weighed 9½ lb. at birth. She had been breast fed till twelve months of age and then had a good mixed diet. Her mother and father were alive and well and she had one healthy sister aged six years. The maternal grandfather had pulmonary tuberculosis and the patient had frequently been taken to visit him.

She had been quite well till six weeks before admission, and then she became fretful, ' off colour,' and slowly lost weight. Three weeks ago she had ' gone off her legs,' although she had begun to walk when aged nine months. For the last seven days she had refused all solid food and vomited nearly all fluids. During that week she had only one constipated stool with the help of an enema. Her mother had noticed that while lying in bed she would suddenly scream, and this screaming was followed by prolonged crying. She had had no rash, no convulsions, no aural symptoms or disturbance of micturition and no cough. The mother did not think she had been feverish but she had become more and more fretful and miserable.

On examination the infant was pale, flabby, wasted and very unhappy. The temperature was normal. The anterior fontanelle was closed. There were no abnormal physical signs. Miliary tuberculosis with tuberculous meningitis was suspected, and an x-ray of the chest showed a small opacity at the left apex. The case was therefore diagnosed as one of tuberculous meningitis with the primary focus in the apex of the left lung.

Lumbar puncture gave a turbid, yellow fluid under considerable pressure and the laboratory gave the following report on the cerebrospinal fluid :

PROTEIN. 240 mgm. per cent.
SUGAR. No reduction with Benedict's solution.
CHLORIDES. 705 mgm. per cent.
CELLS. 750 per c.mm.
Polymorphonuclears 55 per cent.
Lymphocytes 45 per cent.
FILM STAINED BY GRAM'S METHOD. A few extra-cellular meningococci seen.

This was a surprising result, but the blood count also showed an excess of polymorphonuclears. The total white blood cells numbered 14,500 per c.mm., the polymorphonuclears 56·5 per cent., and the lymphocytes 39·5 per cent.

It was presumed that the case was one of missed meningococcal meningitis now in the chronic stage and that the x-ray appearance of the chest was a coincidence. The infant was given sulphapyridine by mouth slightly in excess of the dose given in the table by Hynes (1940). Next day the temperature had risen to 100° F., but the child had stopped vomiting and was taking solid food, although she was still miserable and there was a suspicion of neck rigidity. Lumbar puncture gave a fluid which was still turbid, and had a pressure of 170 mm., which rose to 240 mm. on crying. About 20 c.c. of this fluid was removed. There was no change on the third day and the slight stiffness of the neck persisted. A tuberculin patch test and a Mantoux 1 in 100 gave strongly positive results, but it was decided to investigate the chest more thoroughly after the meningitis had been treated.

On the fourth and fifth days the temperature remained raised but the infant was much brighter and taking notice. On the sixth and seventh days the temperature rose to 101·6° F., and she became drowsy, with definite neck stiffness. Her white count still showed an excess of polymorphonuclears. The total white blood cells numbered 13,730 per c.mm., the polymorphonuclears 60·5 per cent., and the lymphocytes 32·5 per cent. Lumbar puncture gave a turbid yellow fluid with a drip of normal speed containing :

PROTEIN. 750 mgm. per cent.

CELLS. 642 per c.mm.
Polymorphonuclears 44 per cent.
Lymphocytes 56 per cent.
FILM. No organisms seen.

The child was still having large doses of sulphapyridine, but as it did not seem to be efficacious she was also given 5 c.c. of anti-meningococcus serum intravenously. The temperature then fell to normal for two days, but she was still extremely drowsy and difficult to feed. She began to vomit for the first time since admission. Fluid from the lumbar puncture on the ninth day was not so turbid, but the pressure rose to overflow the manometer. 30 c.c. of the fluid were withdrawn and 10 c.c. of meningococcus antitoxin were injected intrathecally. The report on the cerebrospinal fluid was :

PROTEIN. 200 mgm. per cent.
CELLS. 190 per c.mm.
Polymorphonuclears 35 per cent.
Lymphocytes 65 per cent.

The combination of chemotherapy and antitoxin appeared to be having some effect. The x-ray appearance of the chest had not changed.

On the following day the temperature rose again to 101° F. ; the child vomited and became more drowsy. In the evening she began to twitch down the left side, and this twitching was followed by a convulsion, after which the arms and hands were spastic. She had a bilateral positive Babinski's sign and went into opisthotonos for about thirty seconds. Her pupils, which had never been fully dilated, were now dilated with homatropine and the fundi examined. There was some fullness of both physiological cups and a large tubercle was seen just above the right disc. Later that evening her breathing became stertorous, and she had convulsions followed by opisthotonos every few minutes. Three-and-a-half hours after the onset of the twitching she went into a position of opisthotonos and remained in that position (fig. 1).

A lumbar puncture that evening produced an extremely turbid fluid, more turbid than at the time of admission, but no meningococci nor tubercle bacilli were found. The next day she remained in a state of extreme opisthotonos, with the head almost touching the buttocks when she was disturbed. She was unconscious, and it was impossible to feed her. The temperature remained above 101° F., with a pulse of 180 per minute. The following day, the twelfth after admission, the temperature rose to 105° F., the pulse to over 200, and she died, having been in opisthotonos for forty hours. Spasticity of the arms was persistent during this time but the legs only became spastic when she was disturbed.

Post-mortem examination. The body was that of a thin female infant. The brain was first examined and weighed 975 grammes. The external appearance was interesting, as two types of exudate were present in the meninges. On the ventral surface of the cerebellum and stretching forward to the pons was a thick, greenish-yellow, purulent exudate. Covering the mid-brain and crura cerebri, and running into the cerebral sulci, along the vessels, was a much thinner, whitish exudate containing many miliary tubercles, especially about the vessels of the Sylvian fissure. There was a great excess of cerebrospinal fluid in the ventricles. The brain was fixed, and when examined later both lateral ventricles were greatly dilated and many miliary tuberculomata were seen in their walls. In the left optic thalamus, at the level of the genu of the corpus callosum, a tuberculoma 1 mm. in diameter was found. Another minute one was present in the white matter of the second left frontal convolution. On the right side of the brain, a tuberculoma, identical in size and situation with that on the left side, was in the optic thalamus. A minute one was also present just above the middle of the body of the right lateral ventricle.

The surfaces of the lungs were free from miliary tubercles and the right lung was normal. The bifurcation and tracheobronchial glands were not enlarged. In the left lung a primary focus, measuring $2 \times 1{\cdot}5$ cm. in diameter, was found bordering on the apex of the upper lobe, but no miliary tubercles were present. On the posterior surface of the left lung, attached to the pleura, was one caseous gland in the situation corresponding to that of the so-called ductus arteriosus gland. This was the only mediastinal gland affected by the tuberculous process.

The heart was normal. The liver showed fatty change but no tubercles were found on or in it. The spleen was covered with tiny miliary tubercles but none

FIG. 1.—Position of opisthotonos in which child remained for 40 hours. Taken 24 hours before death.

was seen in its substance. Two tiny tubercles were seen in the cortex of the left kidney. The right appeared normal, as were the suprarenals. The stomach was normal, but one small tuberculous ulcer, the size of a pin's head, was found in the terminal portion of the ileum. There was no enlargement of the mesenteric glands.

Discussion

This case was interesting both as a rarity and as an unusual problem in diagnosis. It was unfortunate that the original clinical diagnosis was discarded because of the indisputable pathological diagnosis, but the physician is trained to abhor the double diagnosis. The diagnosis of a combined form of meningitic infection might have been made sooner had the choroid tubercle been seen on admission. The treatment of the case, while believed to be

meningococcal meningitis, was orthodox in that large doses of sulphapyridine were given and lumbar punctures performed to note progress. Blood counts were done every few days to make sure that the sulphapyridine was not having a deleterious effect. Anti-meningococcus serum and antitoxin were given while the final diagnosis was still unmade.

The order in which the infections occurred can be surmised from the post-mortem examination. The primary tuberculous focus in the lung, which was fibrotic, was presumably acquired some months before, perhaps from the grandfather, and the onset of the tuberculous meningitis was, no doubt, six weeks before the child was seen at hospital when a change was first noticed. The intracranial tuberculosis must have been present for some time, judging by the tuberculomata in the substance of the brain and the many miliary tubercles on the surface. The child might have been a carrier of the meningococcus in the throat, and, presumably, this organism only became sufficiently virulent to cause meningitis about a week before the patient was admitted.

Two other unusual aspects of the case were, first, that the pus in the cerebrospinal fluid from the post-basic suppurative type of meningitis increased greatly just before death in spite of the fact that the sulphapyridine had not been withdrawn ; and, second, that the opisthotonos, or 'gun-hammer' position, was of such severity and sustained for so long.

Thanks are due to Dr. R. S. Frew for permission to report this case, to Dr. Ruby O. Stern for the pathological investigations, performing the post-mortem examination and for much helpful advice, and Mr. Derek S. Martin for taking the photograph.

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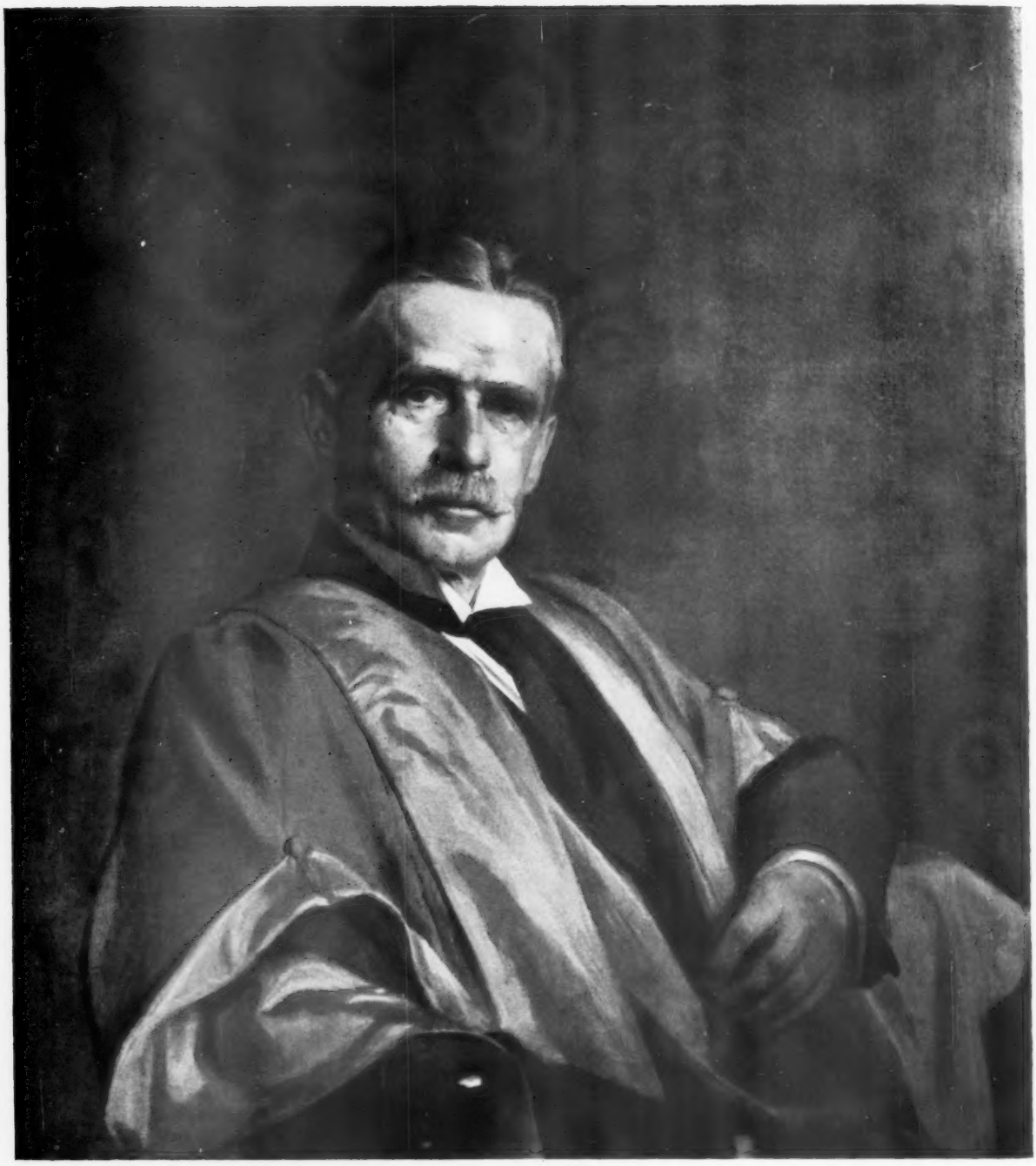

FROM THE PORTRAIT BY GERALD F. KELLY, R.A.

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IN MEMORIAM

GEORGE FREDERIC STILL, 1868–1941

In many of our older schools and colleges there is in daily use a bidding prayer which commemorates the Founder : and it is fitting that a like commemoration should be made to one who, if not the Founder, was an ardent supporter and tireless worker in the earlier and more troubled days of ' The Archives of Disease in Childhood ', and gave unstinted service as Chairman of its Editorial Committee from its birth until quite recently, using his influence and his ideals in the promotion of a scientific publication in this special branch of medicine. It is therefore in the words of the bidding prayer ' fitting and our bounden duty ' to celebrate his memory.

George Frederic Still was born in 1868, a Londoner of a family of that middle class from which so many of her finest citizens have sprung. He was educated at Merchant Taylors', whence he proceeded to Caius College, Cambridge, as a classical scholar. At Cambridge he won distinction as a classic and took his degree in the Classical Tripos with first-class honours, and passed on to a career in medicine. From Cambridge he went to Guy's Hospital and there came under the influence of James Goodhart, to whose teaching and example he owed in some part his inclination towards the study of disease in children. In 1894 while still at Guy's he won the Murchison Scholarship, awarded after examination in clinical medicine by the University of Edinburgh and the Royal College of Physicians of London in alternate years. From Guy's, following his bent, he became House Physician at The Hospital for Sick Children, Great Ormond Street, and began a connexion which lasted for more than thirty years. In his earlier years there he produced two pieces of work which established his reputation as a scientific observer ; his thesis for the Cambridge M.D. degree on ' A special form of joint disease met with in children,' an accurate clinical and pathological account of what has become widely known as ' Still's disease ' (his original article is reprinted elsewhere in this issue) : and the identification of the organism responsible for the affection described clinically many years previously by Gee and Barlow as posterior basic meningitis. After some years of fruitful work as medical registrar in the wards and laboratories of Great Ormond Street, Still was elected to the staff, and in the same year was appointed Physician for Diseases of Children at King's College Hospital, the first of the general hospitals of London to establish a special department in this branch of medicine. Seven years later he became the Professor of the Diseases of Children at King's College, the first man to whom that title was granted in the United Kingdom. In the meantime Still had been steadily adding to his reputation by his writings. He had

collaborated with Goodhart in the later editions of that physician's successful text-book on the diseases of children, and afterwards produced more than one edition unaided. At the same time he was publishing on his own account articles, papers and lectures, nearly all on the clinical or pathological aspects of disease; and many of these have a permanent value, for he was an acute and accurate observer. In 1909 he published in his own name 'Common Disorders and Diseases of Childhood' a work which embodied much of his own first-hand experience, made possible by his habit of maintaining and constantly analysing elaborate notes of all his clinical cases, both in hospital and private work. This book is in the opinion of many good judges the best and most trustworthy guide to clinical paediatrics yet published. By this time Still was beginning to enter upon a period of busy and lucrative private practice as a consultant, and in the ensuing years he became so much the recognized authority that it was difficult to find any child of the more educated and wealthier class of the community who had not at some time been taken to see him. Yet busy as he was he always, like all true physicians, freely and generously gave his services to many who could not afford a consultant's fees. In this round of busy practice and busy authorship Still never neglected his hospital work, either, needless to say, the work of the wards and out-patient rooms which lay nearest to his heart, or that less attractive but essential business of committee work, and the organization of teaching at both his hospitals. At King's he was for three years the Chairman of the Medical Committee, and those who know what the work of the Medical Committee of a teaching hospital implies will realize how great a burden such an office brings in expenditure of time and energy. Moreover, he shouldered willingly and in his usual thorough fashion activities in connexion with Dr. Barnardo's Homes, with the Society for Waifs and Strays and the National Association for the Prevention of Infant Mortality. Of this he was Chairman for twenty years, and it owed much to him. In 1926 he reached the period of retirement from the active Staff at Great Ormond Street and became Consulting Physician, and in 1934 he became Emeritus Professor at King's. In 1933 the International Paediatric Congress met in London and Still was naturally its President. The President of the Congress was generally recognized not only as a famous and honoured physician, but revealed even to his own profession in this country an hitherto unsuspected geniality of address, and a happy turn of public speaking. His reputation was at its height and the knighthood and appointment as Physician Extraordinary to the King were a recognition of his pre-eminence.

Such in brief outline and with many omissions was the public career of this distinguished physician. To enumerate in detail the honours which fell to his lot whether at the Royal College of Physicians or in the Academies and Societies of the medical world, would be to compile a somewhat featureless catalogue. Rather would it seem better to attempt to set down some of the characteristics which marked the man. In his earlier years in the profession he was so absorbed in his work and so anxious, in Kipling's phrase, 'to fill the unforgiving minute with sixty seconds' worth of distance run', that he often gave the impression to his contemporaries that he

was unused to, and careless of, the courtesies and amenities of ordinary social life ; an impression which even in those laborious days was at once corrected when one came into closer contact with him. Yet even if for a few minutes he relaxed he would quickly recollect himself, as if he heard ' Time's wingèd chariot hurrying near ', and the momentary glimpse of his scholarly and genial spirit was lost in the business of the hour. He was then no lover of sports, but in his later years became, somewhat to the amazement and amusement of his friends, an ardent, but, as he himself owned, an inefficient dry-fly fisherman. He would at that time, I imagine, have justified his addiction by the example of gentle Izaak Walton, but after some years lost his enthusiasm for the sport. He never, so far as I know, acknowledged the cause of the change, but more than once it appeared from sundry hints and allusions that it was due to an increasing unwillingness to take life in any form. That is often a factor in the abandonment of shooting in men of increasing age, but is rare among the haunters of the Test or Itchen. His social gifts were seen at their best in the gatherings of the College Club. In that congenial atmosphere among men who knew him well and whom he knew well he expanded and revealed a capacity to enjoy the fleeting hour of relaxation which he seldom showed in everyday life. The classical learning of his earlier days remained fully alive, and his reading was by preference in the older authors, Greek, Latin and English. He was in the habit for many years of expressing his thoughts in verse and some years ago published privately a slim volume of his poetry. This with some added pages he re-edited, and it was published a few weeks before his death. It is the ' parergon ' of an accomplished scholar rather than the inspired utterance of a poet, but it exhibits another side of his mind, the delight which he found in expressing his thoughts within the constraint of an ordered rhythm in carefully studied grace of language.

I cannot end this brief attempt to illustrate his memory better than by quoting the Greek epitaph * written by a modern scholar in memory of another ' blameless physician ' : lines which Still with his love of Greek brevity and eloquence would have appreciated and cherished.

Χαῖρε θάνων, αἰῶν' ἀνύσας ἰσόμοιρον ἐπαίνῳ,
ἐνθάδε μὲν κλαυτὸς, τοῖς δ'ἐκεῖ ἀσπάσιος·
σώμασιν ὃς θνητῶν ἔζης ἰατρὸς ἀμύμων,
πιστὸς τῷ Ψυχῶν πήματ 'Ιαομένῳ.

The ' blameless healer ' of children's ills has passed from among us full of ' Faith in the Supreme Healer of Souls '.

HUGH THURSFIELD, D.M., F.R.C.P.

* A real translation of this epigram is beyond my powers, so packed is it with the Greek genius for the expression of much in the fewest possible words, and in the most allusive phrase.

'Hail, dead friend, who hast run thy course with honour thy constant companion: mourned by us here: welcome to those above: thou didst live a blameless healer of the bodies of mortal men, filled with faith in Him who heals the sins of souls.'

ADDRESS AT A MEMORIAL SERVICE

BY

SIR ROBERT HUTCHISON, Bt., M.D., F.R.C.P.

We are met here to-day, all of us friends and many of us colleagues of George Frederic Still, in testimony of our sorrow at his passing, but also in proud recollection of his work and character. This is not the time to speak of his professional achievements; it is enough to say that he was universally recognized, not only in this country but throughout the world, as a master in that branch of medicine to which he devoted himself. This mastery was the result not only of his great intellectual gifts but also of the unwearied diligence and thoroughness of his work as a children's doctor; it was a triumph of character as much as of brains.

But to-day we would rather think of our friend as we knew him as a man. Shy and reticent we all knew him to be and one who did not wear his heart upon his sleeve, but those whom he admitted to his friendship found him a warm-hearted human being of infinite kindness and generosity. No one, moreover, could know him even slightly without being impressed by the high principles which guided his every action and how impossible it was to associate him with anything common or mean. It is only right, speaking in this place, to recognize that these high principles were deep-rooted in a simple and sincere religious faith, and it is surely fitting that he should have been laid to rest within the precincts of that Cathedral from whose ritual he derived so much joy and comfort in his late years. Like the Master in Whose footsteps he tried to follow he was the friend of little children; he ministered to them in their sickness, he loved them and was loved by them in return and no man can desire a better epitaph than that. Let us then remember his life's labours with thankfulness and let us all, and especially the younger of us, take encouragement from his example.

But our friend was not only a great doctor and man of science, he was also a poet for whom the common things of life were transmuted by the poet's vision. Shortly before his death he published a little book of his poems, mostly, as was natural, about childhood, and I should like to end by reading to you one which sets out very beautifully and simply, the memory of himself which he wished—and which we may all wish—to leave behind. It is called 'Life's Aftermath.'

When I shall die and in the quiet earth
Am laid to rest,
Will there remain some breath of aftermath
Of worst or best,
Some potency of evil or of good,
Its source unguessed,
From words or deeds, remembered or forgot,
A life's bequest?

God in his mercy grant that all the wrong
May cease to be,
Not only be forgiven but blotted out,
That so of me,
Shall nothing live that might work other's ill,
No legacy
Of harm to lead one single soul astray,
—Thus may it be,
When I shall die.

Can any of us who knew and loved him doubt that so it will indeed be with him as long as his memory remains ?

GEORGE FREDERIC STILL

BY

PROFESSOR CHARLES McNEIL, M.A., M.D.

President, Royal College of Physicians, Edinburgh; President, British Paediatric Association

The working life of Sir Frederic Still coincided with an important development in paediatrics—its establishment as a separate field of clinical study and practice; and his own work as clinical investigator, teacher and writer, was a notable contribution to that development. In 1930 he published his ' History of Paediatrics,' and brought the story to the end of the eighteenth century. When in due time the story has been brought up to date, it will be seen that Still, the medical historian, has written by his life and work another chapter in the book. When he went to Great Ormond Street Hospital in the 'nineties of last century, that pioneer institution was only forty years old, but it had been served by a succession of great physicians, and the foundations for further progress had been well laid; and in every important phase of subsequent development, Still's influence can be seen. His great abilities, and his power of detailed accurate work were concentrated on this branch of medicine. The special problems of the child had now been studied in the hospital; and the next steps were their discussion in the club and society, and their teaching in the schools. We find Still, as a young man, Secretary of the Children's Clinical Club, which met in London twice a year, and included among its members Barlow, Eustace Smith, Coutts, Lees, William Osler, John Thomson and Henry Ashby. Still, a trained and careful recorder, kept full minutes of the proceedings, and these minutes may well be useful documents for the future medical historian. In 1906 a more outward sign of growth appeared in his appointment as Professor of Diseases of Children at King's College. Progress was now opened up along both the paths of teaching and critical discussion; and when in 1928 the British Paediatric Association was founded, the choice of its first president naturally fell on Still, now praeclarum et venerabile nomen in British paediatrics. The new Association was strong in itself, in the enthusiasm and good fellowship of its members; and the first meeting was well launched by the reputation and dignity of its president, who in spite of his reserve and reticence in ordinary social intercourse, was ready and well equipped in any technical discussion, and could give to a ceremonial speech the finish and distinction of his literary scholarship. This well-founded clinical reputation, these gifts of mind and speech, were also shown to advantage when he presided at the International Paediatric Congress in 1933.

Thus in his own clinical work, in his teaching and writing, and in the impact of his work upon others, he was a powerful force in the development of paediatrics in his time. Many others had a share in this development, but he was an outstanding figure. His influential masters were Barlow and Goodhart; he received from them the sound broad clinical tradition of English medicine, and he has handed on that good tradition to his students and successors. And perhaps in his case the teaching he gave by example was even more important than that of precept—the example of patient, thorough, accurate clinical work, of fastidious care in his writing begotten of his classical training; and of his strong and upright character, reserved towards his fellow men, but showing its tenderness and playfulness in his contact with children.

In his last literary testament, ' Childhood and other Poems,' published just before his death, Still sprang a surprise on his contemporaries, and showed that he had in his many-sided personality a vein of poetry, and one that he must have worked unobserved for many years. It is not unlikely that these verses will keep a place in English literature for they bear not only the stamp of scholarly workmanship, but also of a deep feeling for children. And in English medicine his ' History of Paediatrics ' will certainly survive, whatever may be the fate of his other medical writings. As for that part of a man's work that is unrecorded, but passes into the texture of other minds and bears fruit in their actions, the name and work of Still will endure. His work was done at a time when a new phase in paediatrics was beginning: and in that phase he played a leading part, receiving the tradition of older physicians, moulding it, and handing it on to his successors. Quasi cursores tradunt lampades. Still loved the classical brevity: both as a scholar and a man he would be content with these four Latin words for his epitaph.

A HANDLIST OF THE WRITINGS OF GEORGE FREDERIC STILL

Compiled by ALFRED WHITE FRANKLIN, M.B., M.R.C.P.

This handlist is presented as a slender tribute to a pioneer—the first English doctor to devote his life to the study of disease in children. Still's writings record with living individual touch the medical opinions of one who, born into the clinico-pathological tradition of nineteenth-century medicine, helped in the struggle for sound etiological diagnosis and saw the dawning of the age of rational treatment.

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Sir Frederic Still edited and prefaced the King's College Hospital Pharmacopoeia for 1901, 1916, and 1927.

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ON A FORM OF CHRONIC JOINT DISEASE IN CHILDREN

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The occasional occurrence in children of a disease closely resembling the rheumatoid arthritis of adults has been recognized for several years. The identity of the disease seen in children with that in adults has never, so far as I am aware, been called in question.

The purpose of the present paper is to show that although the disease known as rheumatoid arthritis in adults does undoubtedly occur in children, the disease which has most commonly been called rheumatoid arthritis in children differs both in its clinical aspect and in its morbid anatomy from the rheumatoid arthritis of adults; it presents, in fact, such marked differences as to suggest that it has a distinct pathology.

The cases hitherto grouped together as rheumatoid arthritis in children include, therefore, more than one disease; and it will be shown that there are at least three distinct joint affections which have thus been included under the one head, rheumatoid arthritis.

The paper is based on a study of twenty-two cases, almost all of which have been in the Hospital for Sick Children, Great Ormond Street. Nineteen of these I have had under personal observation.

It will be necessary first to describe briefly the disease to which I have referred as the subject of this paper, and subsequently to point out the features of its clinical course and morbid anatomy, wherein it differs from the rheumatoid arthritis of adults.

The disease may be defined as a chronic progressive enlargement of joints, associated with general enlargement of glands and enlargement of spleen.

The onset is almost always before the second dentition; ten out of twelve cases began before the age of six years, and of these eight began within the first three years of life: the earliest was at fifteen months.

Girls are more commonly affected than boys; seven of the twelve cases were girls, five were boys.

The onset is usually insidious; the child, if old enough, complains of stiff-

ness in one or more joints, which slowly become enlarged, and subsequently other joints become affected; but occasionally the onset is acute, with pyrexia and, it may be, with rigors.

I wish to lay some stress on the character of the enlargement of the joints. It feels and looks more like general thickening of the tissues round the joint than a bony enlargement, and is correspondingly smooth and fusiform, with none of the bony irregularity of the rheumatoid arthritis of adults.

The absence of osteophytic growth and of anything like bony lipping, even after years have elapsed since the onset, is striking.

There is, I believe, never any bony grating, although creaking, probably either of tendon or of cartilage, is frequently present. There is no redness or tenderness of the joints, except in very acute cases. The absence of pain is generally striking, but it may be present in slight degree, especially on movement. Limitation of movement, chiefly of extension, is almost always present; the child may be completely bedridden owing to more or less rigid flexion of joints.

The extensive deformities of the hands described by Charcot as occurring in the rheumatoid arthritis of adults ('Maladies des Vieillards,' 2nd edit., p. 201) are unknown to me in this disease. Those most common so far as I have seen are, flexion of the wrist with slight deviation of the hand to the ulnar side, and slight flexion of the proximal, combined sometimes with slight flexion of the distal, inter-phalangeal joint. Rarely there is slight hyper-extension of the metacarpo-phalangeal or proximal interphalangeal joint. The fingers may deviate very slightly to the radial side, but more often the deviation is at the proximal inter-phalangeal joint, and may be to either side; indeed, both directions may be seen in one hand. Adduction of the thumb was marked in one case.

The joints earliest affected were usually the knees, wrists, and those of the cervical spine; the subsequent order of affection being ankles, elbows and fingers. The sterno-clavicular joint was affected in two out of twelve cases; the temporo-maxillary in three. The affection is symmetrical. There is no tendency to suppuration nor to bony ankylosis. The muscles which move the diseased joints show early and marked wasting, which contrasts often strongly with the good nutrition of the rest of the body.

The electrical reactions both to faradism and galvanism were brisk in three cases tested, but not otherwise altered.

Perhaps the most distinctive feature in these cases is the affection of the lymphatic glands. The enlargement is general, but affects primarily and chiefly those related to the joints affected. The glands are separate, rather hard than soft, not tender, and show no tendency to break down. They may become so large as to be visible, but more often do not become larger than a hazel-nut. The enlargement seems to bear a definite relation to the progress of the disease in the joints. Slight affection of the glands is found very soon after the first symptoms of the joint affection, and as the latter increases the glands become larger. If the joint affection subsides, the glands become smaller, increasing again in size if the joints become worse.

The glands most affected are the supra-trochlear, those along the brachial artery, and those in the axilla, also those in Scarpa's triangle, and deep in the iliac fossa along the iliac artery, and those in the posterior triangle of the neck. In one case I thought that the popliteal glands were enlarged, and in two cases there was some evidence clinically of enlarged mediastinal glands. I have never been able to make out enlargement of mesenteric glands, but in one of the autopsies which I shall mention, the glands in the hilum of the liver were found enlarged.

It will thus be seen that the enlargement is general; and I may add that it is constant; it was found in all the twelve cases mentioned.

Enlargement of the spleen is also a striking feature of these cases. It is, of course, not always easy to be certain of splenic enlargement, but it was definite and considerable in nine out of the twelve cases, the edge of the spleen being felt one to two fingers' breadth below the costal margin. The enlargement of the spleen seems to be roughly proportionate to that of the glands, and like that of the glands has been observed to increase as the joint condition became worse.

The heart shows no evidence of valvular disease, but haemic bruits were detected in some of the cases.

There were some physical signs suggestive of adherent pericardium in two of the twelve cases, and in three other cases adherent pericardium was found quite unexpectedly at the autopsy.

Anaemia is generally present to some extent, but is seldom profound; the face has often a curious waxy pallor with flushed cheeks. The blood shows only moderate diminution of red corpuscles in most cases; in some, however, there is disproportionate deficiency of haemoglobin.

A curious symptom noticed in four cases out of the twelve, was slight prominence of the eyes, hardly enough to call exophthalmos, but enough to be noticeable. The thyroid seemed normal in the cases which I examined.

Sweating is often profuse, and not related to temperature. The temperature seems to be of two varieties: the one shows periods, generally lasting only a few days, of pyrexia followed by a longer interval of apyrexia; the other shows more or less continuous slight pyrexia. The pyrexial attacks occasionally show a curious regularity in their recurrence. One or two cases showed sudden attacks of hyperpyrexia, lasting one hour or two, and then subsiding rapidly. The pyrexial periods are not usually associated with any clinically demonstrable exacerbation of the joint trouble, nor indeed is it possible usually to find any definite cause for the fever.

I have made a detailed study of the urine in these cases, and find that the urea, uric acid, phosphoric acid and chlorides each show considerable variations, but that these variations are within the limits of health, as shown by a series of analyses of the urine from healthy children. The urine in other respects also was normal.

A remarkable feature in these cases is the general arrest of development that occurs when the disease begins before the second dentition. A child of twelve-and-a-half years would easily have been mistaken for six or seven

years, while another of four years looked more like two-and-a-half or three years.

The arrest is, however, of bodily rather than of mental development, and hence although backward in some respects from the enforced absence from school, the child often appears by comparison with its size to be rather precocious than backward.

The course of these cases is slow. Improvement may occur for a time under treatment or spontaneously, but the disease soon progresses again until a condition of general joint disease is reached which seems to be permanently stationary. The disease is not in itself fatal; the few deaths that have been recorded were due to complications.

Curiously enough, some accidental complications have been followed by marked improvement; thus I have known measles, scarlet fever and catarrhal jaundice, to be each followed by distinct improvement of the joint symptoms.

The etiology of the disease is very uncertain. A careful investigation of the family history in ten cases gave the following figures: phthisis in five, acute rheumatism in four, rheumatoid arthritis in one (a grandmother), gout in none, syphilis in none. The frequency of acute rheumatism and phthisis here cannot be considered to have any special significance; a similar investigation of fifty consecutive non-rheumatic, and also of fifty non-tubercular cases in the Hospital for Sick Children gave respectively 44 per cent. and 46 per cent. as the number of times that acute rheumatism and phthisis occurred in the family history.

No relation to diet in infancy could be shown. Poverty and exposure to insanitary conditions seemed to play little if any part in its causation.

The morbid anatomy of this disease is gathered from three post-mortems. (I unfortunately did not see these myself, so that my information is obtained from the post-mortem records, corroborated by those who saw the autopsies.) For permission to make use of the record of one of these cases I am indebted to the kindness of your President, Dr. Dickinson.

The joints show marked thickening of the capsule and of the connective tissue just outside this. There is also thickening and vascularization of the synovial membrane, and fibrous adhesions are sometimes present.

The cartilage may be perfectly normal, as in two cases that had lasted nearly one-and-a-half years; but in a case that had lasted three years it showed pitting of its surface as if from pressure, with little processes of the thickened synovial membrane fitting accurately into the pits, which were situated chiefly at the margin of the cartilage; otherwise, however, the cartilage was healthy—there was no fibrillation, no osteophytic change, no exposure or eburnation of bone.

The enlarged glands appear normal on section, or show small ecchymoses in their substance.

The spleen weighed in each case about 5 oz., so that it was considerably enlarged; it was firm, and appeared normal on section.

In each case the pericardium was universally adherent; there were also pleural adhesions. There was no endocarditis certainly in two cases, but in the third the mitral valve was perhaps a little thickened.

The following case, under the care of Dr. Lees at the Hospital for Sick

Children, Great Ormond Street, may serve to illustrate some of the points mentioned.

Alice C., at the age of two years and four months began to limp in walking, and it was noticed that the ankles were swollen. A week or two later the elbows, and then the knees, became stiff and swollen; stiffness of the neck also was noticed almost from the first onset. The joints affected became steadily worse, and the child quickly lost the power of standing.

Chronic arthritis, with enlargement of glands and spleen.

FIG. 1.—Alice C., aged 4 years; showing tendency to fixation of joints in position of flexion.

There had been no previous illness, except whooping-cough; the child had been carefully hand-fed after it was four weeks old; up to this time it had been breast-fed. There had been no privations, but the house was damp. The family history showed nothing of importance except a doubtful history of rheumatism in two maternal uncles.

When first seen at the age of three-and-a-half years, the child was fairly nourished, with round face and slightly prominent eyes. All the joints of the limbs were affected; extension of the knees, hips and elbows was considerably limited, there was thought to be a little fluid in the knees, ankles and wrists,

and there was obvious fusiform elastic thickening of all these joints except the shoulders and hips. I could not find any definite bony enlargement, and there was no grating. The sterno-clavicular and temporo-maxillary joints, and dorsal and lumbar spine, were unaffected.

Gland enlargement was marked; the axillary, supra-condylar, cervical, iliac and inguinal were affected; the axillary were easily visible. The glands were hard, separate, and not tender.

The spleen was one finger's breadth below the costal margin. Heart and lungs were normal.

For nearly two years the child has been in the Hospital for Sick Children, and the joint condition has slowly become worse (as will be seen from the photograph shown), so that the child is unable even to turn herself in bed. The progress of the disease has, however, not been steady; at one time there was a slight improvement in the joint condition, and synchronously with this the glands and spleen became much smaller.

The temperature chart has shown the recurrent attacks of pyrexia described above.

Having sketched the clinical aspect and morbid anatomy of the disease, I wish now to draw attention to the points in which the condition differs from the rheumatoid arthritis of adults.

The clinical features of the joint affection cannot be considered distinctive, but it may be pointed out that the fusiform enlargement which feels like extra-articular thickening of soft tissues, and the absence of bony lipping and grating, even after the disease has lasted some years, are very unlike the irregular bony enlargement of joints found in the advanced rheumatoid arthritis of adults.

Pathologically, however, the joints show marked differences. In the children's disease there is complete absence, even in an advanced case, of the cartilage changes which are seen quite early in the rheumatoid arthritis of adults. In the children's disease, also, there is a very considerable thickening of the capsule, and of the connective tissue just outside this, which is a much less prominent feature in the disease of adults.

On the enlargement of glands I lay great stress. It is, I think, one of the most important points of distinction clinically between this disease and rheumatoid arthritis. It is, as far as I know, never found in the rheumatoid arthritis of adults, whereas it is a constant symptom in the disease of children here described.

The enlargement of the spleen, associated with the glandular enlargement, is another important distinction, and like the preceding symptom is, I believe, unknown in adults.

Other minor differences are the following:

The incidence on the sexes is different. The proportion of females to males affected by rheumatoid arthritis in adult life was found by Sir A. Garrod to be 5 : 1, whereas in the disease described above the proportion is barely 1·5 : 1; my numbers, however, are so small that no great weight can be attached to this difference.

The order of affection of joints is different. In adults rheumatoid arthritis affects the small joints of the hands quite early, and often begins here; whereas the disease of children begins nearly always in the knees or wrists, and the fingers

remain often free for months or even years. The very early and almost constant occurrence of affection of the cervical spine is also, I fancy, far more common in the disease here described.

Lastly, the occurrence of adherent pericardium, certainly in three, probably in five cases out of twelve, with no clinical evidence of endocarditis in any case, and only a slight thickening of the mitral valve of very doubtful significance found post-mortem in one case, and also the occurrence of pleurisy in four out of twelve cases, suggests some peculiar liability of children with this disease to inflammation of serous membranes, a liability which is not shared by the rheumatoid arthritis of adults.

From the foregoing it is seen that there are well-marked clinical and pathological differences between the rheumatoid arthritis of adults and the disease of children above described. But when it is suggested that the two conditions are therefore different diseases, it may be objected that the points of distinction mentioned may all be due merely to the difference of age.

This objection seems to me sufficiently answered by the fact that there occurs in children, rarely indeed, but only rather more rarely than the disease here described, a condition which appears to be identical in every respect with the rheumatoid arthritis of adults.

I shall now deal briefly with the second point, namely, that the cases hitherto grouped together as rheumatoid arthritis in children include at least three distinct conditions.

The least rare is the disease already described, which for the reasons I have given should not be called rheumatoid arthritis.

Next in frequency is a joint affection which cannot be distinguished from the rheumatoid arthritis of adults. It is unnecessary to describe it. It presents the same general enlargement of joints, with subsequent bony thickening and lipping, and bony grating as in adults. There is no enlargement of lymphatic glands or spleen, and no evidence of pericarditis.

Of the twenty-two cases, six were of this nature, and the age at onset was generally rather higher than in the preceding disease; two began before the second dentition, one at one year and eight months.

(In the photograph shown by kind permission of Dr. Cheadle, the contrast is seen between the fusiform enlargement of the phalangeal joints in the first disease, and the bony enlargement of rheumatoid arthritis.)

The third condition that has, I venture to think, been confused with rheumatoid arthritis is a form of rheumatism. It is extremely rare. I have seen only one case. It was in a boy, aged five years, under the care of Dr. Lees at the Hospital for Sick Children.

At the age of three-and-a-half years the fingers became stiff, apparently from the formation of fibrous nodules over the tendons. Then the elbows and wrists slowly enlarged, and their movements became limited. There was also some stiffness of the neck. There was no tenderness of joints, and no acute illness at any time. Seen one-and-a-half years later, the elbows and wrists showed firm thickening, very suggestive of extra-articular fibrous thickening. There was none of the fusiform elastic enlargement of the phalangeal joints

which was seen in all the advanced cases of the disease described in the earlier part of this paper; indeed, there was no evident affection of the phalangeal joints, although there was marked limitation of movement, the terminal phalanges being flexed, and some of the proximal phalanges hyper-extended.

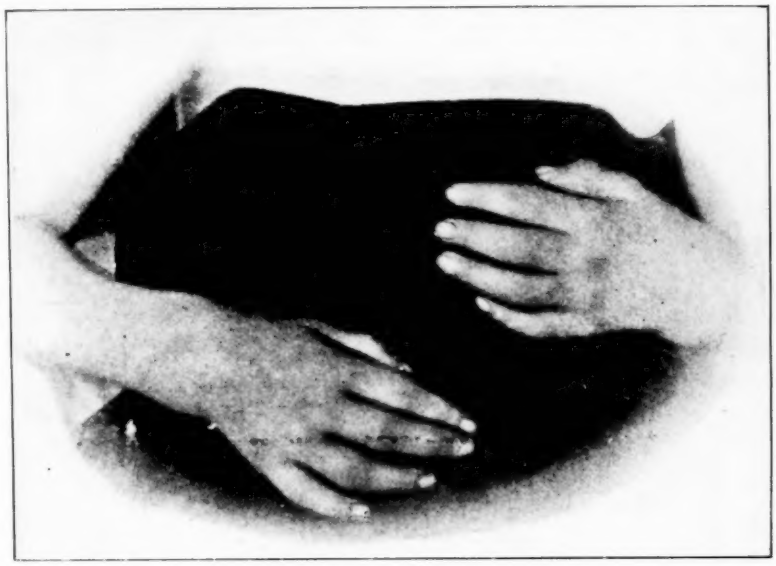

FIG. 2.—Hands of girl aged 7 years, showing fusiform enlargement of joints in the form of chronic arthritis described, with enlargement of glands and spleen.

There was a loud apical systolic bruit; there was no enlargement of spleen or glands. Subcutaneous fibrous nodules were present on the fingers, elbows and head.

In this particular case, although there was no history of acute rheumatism, the association of a cardiac bruit with fibrous nodules was, I think, sufficient proof of the rheumatic nature of the joint affection; but in cases where such additional symptoms were not present to aid the diagnosis, the disease might

FIG. 3.—Hand of boy aged 10 years, showing bony thickening of joints in rheumatoid arthritis.

easily be mistaken for an early rheumatoid arthritis. There can, I think, be no doubt that it is identical with the disease described by Jaccoud (art. ' Polyarthrite Déformante,' *Pathologie Interne*, 1871) as chronic fibrous rheumatism.

It is particularly interesting to note that although Jaccoud described the condition as a disease of young adults, and occurring after repeated attacks of

rheumatic fever, in the case I have mentioned the disease began at three-and-a-half years of age, and there was never any acute rheumatism.

The points of difference between this and the preceding conditions are the following: The evidence of rheumatism, and this is the most diagnostic feature when present, distinguishes it from both the previously described diseases. The absence of bony thickening and of bony grating, and the character of the

FIG. 4.—Girl aged $3\frac{1}{2}$ years; disease began at $2\frac{1}{2}$ years.

FIG. 5.—Jane R., aged 4 years; disease began at the age of 15 months.

Chronic arthritis, with enlargement of glands and spleen.

joint enlargement, which strongly suggests extra-articular fibrous thickening, and I think also the much less likelihood of affection of the small joints of fingers and toes, distinguish this disease from rheumatoid arthritis in children; while the absence of gland and spleen enlargement, and probably here also the less likelihood of affection of the small joints, distinguish it from the disease described in the first part of this paper.

In conclusion, I should like just to mention another affection which I have known raise the question of rheumatoid arthritis in a child. It is a rare form of syphilitic joint disease. It shows, in addition to the commoner chronic effusion with thickening of capsule in medium-sized and larger joints, definite bony thickening and lipping, which affects also the smaller joints; this osteo-

phytic change may even simulate Heberden's nodes, as I have seen in a boy six years old, in whom some of the distal phalanges showed lateral thickenings very like Heberden's nodes. They were, however, less regular in their distribution, for they occurred not only on the distal, but also on one or two of the proximal phalangeal joints, and the toes showed similar nodosities. In this boy the larger joints showed chronic effusion, with some thickening of surrounding soft tissues, and there was a gumma over one ulna, and further evidence of syphilis was found in old iritis. There was no enlargement of glands or spleen.

It may be useful to sum up the conclusions arrived at in this paper.

There is a disease, occurring in children, and beginning before the second dentition, which is characterized clinically by elastic fusiform enlargement of joints without bony change, and also by enlargement of glands and spleen.

This disease has hitherto been called rheumatoid arthritis, but it differs from that disease in adults, clinically in the absence of bony change, even when the disease is advanced, and in the enlargement of glands and spleen, and pathologically in the absence, even in an advanced case, of the cartilage changes which are found quite early in that disease, and also in the absence of osteophytic change.

These differences are not to be attributed merely to modification of disease by difference of age, as there occurs also in children a disease in every respect identical with the rheumatoid arthritis of adults.

Under the head of rheumatoid arthritis in children, at least three conditions have been confused which are both clinically and pathologically distinct, namely: (1) The joint disease described in the present paper; (2) a disease identical with the rheumatoid arthritis of adults; (3) a disease probably identical with that described by Jaccoud as chronic fibrous rheumatism.

Before ending this paper, I wish to express my gratitude to Dr. Barlow, Dr. Lees, Dr. Penrose and Dr. A. E. Garrod, not only for kind permission to use their cases, but also for allowing me to bring forward this subject. They have, I know, taken great interest in these cases for several years, especially in the disease mentioned in the earlier part of this paper, and therefore several of the points which I have described had been already observed by them. I have to thank them for drawing my attention to some of these points, and for allowing me to make use of their observations. To Dr. Garrod I am indebted also for many valuable criticisms and suggestions.

Since the above paper was written, two French observers, Chauffard and Ramond (*Revue de Méd.*, May, 1896), have described occasional enlargement of the lymphatic glands in adults with an acute form of rheumatoid arthritis, which they distinguish as ' infective arthritis '; similar cases have been observed by Drs. Bannatyne and Wohlmann of Bath (*Lancet*, April, 1896). The disease, however, which I have described seems to differ in several points from the conditions described by these observers.

CALORIE REQUIREMENTS OF FULL-TERM AND PREMATURE INFANTS IN THE NEONATAL PERIOD

A FORMULA, ITS USES AND LIMITATIONS

BY

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Medical students and nurses in children's hospitals are now taught how to calculate the calorie needs of babies past the neonatal period, and every textbook on paediatrics deals with the subject; but of the day to day needs of the first weeks of life of babies, varying in birth-weight from 2 lb. to 10 lb. and more, textbooks give meagre and conflicting information.

Some current teaching on quantitative food requirements in the first two weeks of life

Some examples, chosen almost at random, of the teaching furnished in textbooks are given below.

Von Reuss (1921) in his book on 'Diseases of the Newborn,' which is still a standard work, gives numerous examples of the widely different quantities of breast milk taken by healthy babies in the neonatal period; he states that a volume providing 50 calories per kilo. (23 calories per lb.) body-weight per day is sufficient for the first eight to ten days. This figure for the average daily intake, derived as it is from a period of rapid change in the quantity of milk secreted, is not, however, very helpful in ordering each day's supply of food. Von Reuss also quotes a formula of Finkelstein's for 'the first days' needs:—(day of life $-1) \times 70$ to 80 gm. This formula, it will be observed, takes no account of body-weight. It provides a total of about 50 calories on the second day of life (assuming the calorie value of the milk to be 20 per fluid oz.), and an increase of about 50 calories daily, presumably reaching 350 calories on the eighth day. Supposing average birth-weight to be approximately 7 lb., this would represent an allowance of 50 calories per lb. birth-weight on the eighth day of life, or an average intake of 25 calories per lb. per day during the first eight days. Most British textbooks give no information as to the quantity of food required by full-term babies in the neonatal period, but Paterson and Forest Smith (1938) say that 25 calories per lb. birth-weight should be given on the second day, and furnish a table of instructions for artificial feeding according to which approximately 50 calories per lb. birth-weight would be given by the fourth day of life instead of the eighth, as in Finkelstein's formula. On this basis the allowance for the whole of the first eight days would average 39 calories per lb. per day, a figure 70 per cent. higher than that (23 calories per lb.) given by von Reuss (1921), and the allowance for ten days would be 45 calories per lb. per day, or nearly double von Reuss's figure. Contrast with this the advice

of Tallerman and Hamilton (1928): they would not give 50 calories per lb. body-weight until the third week, and consider that it is often impossible to give more than 25 to 30 calories per lb. body-weight on any day before the tenth, or Moncrieff's (1940) advice that a bottle-fed baby should have saline only and no food till the third day of life, when he should, according to the author's feeding table, receive about 2 calories per lb. birth-weight, increasing to 50 calories per lb. by the seventh to tenth day. Of three American encyclopaedic works on paediatrics, those edited by Abt (1923) and by Brennemann (1938) apparently give no information as to the quantitative needs of full-term babies at this period, but in 'Clinical Pediatrics,' Wilcox (1928) states that the calorie requirement of babies during the first two weeks is equivalent to an average of 35 calories per lb. per day.

As regards the needs of premature infants textbooks furnish much fuller information, often in the form of tables, but give little indication as to any principle or formula governing the choice of the quantities prescribed, which are remarkably varied. For instance, for a baby weighing 2 lb. at birth, Hess (1922) prescribes, on the second day of life, in all 14 to 28 calories; Owen and Dobbs (1940) 20 calories; Brown (1933) probably 20 calories; Holt and McIntosh (1936) 50 calories, and Paterson (1937) 60 calories—a four-fold variation. Moreover, Holt and McIntosh, as well as Paterson, would give as much or more to a 2 lb. baby of this age as Finkelstein (1921) would give to a full-term baby weighing presumably three or four times as much. For a 2 lb. baby an allowance of about 50 calories per lb. body-weight (i.e. 100 calories in the day) would be reached by Holt and McIntosh by five days old, by Paterson by seven days old, by Dobbs and Owen by about thirteen days old, and by Hess by twelve to eighteen days old.

Appetite as a guide to food requirements

Most writers stress the importance of such factors as appetite and rate of gain in weight in determining quantitative needs. Faber (1922) has analysed the food intake and rate of gain of over eighty babies given the breast and as much supplementary feeding as appetite prompted them to take (see table 3). Taking averages, these babies regained their birth weight (3·35 kilo.) by seven days old, and they showed no sign of digestive disturbance. So that in these respects appetite proved a good guide to quantitative needs, though, as Faber points out, slightly less milk was taken from the breast by the babies offered unlimited bottle feeding compared with those fed at the breast only, and Faber specifically states that he does not advocate this system for general use. Though it is true that the normal baby, having a normal mother with normal lactation, will satisfactorily regulate his own consumption of breast milk; yet if all is not going well in the neonatal period, the baby's appetite often gives scant guidance as to his needs. Mistakes in the feeding of full-term new-born babies are certainly common, but quantitative errors in the feeding of premature babies are still more common, and with a small premature baby appetite gives little or no guidance as to the needs of the first weeks.

Purpose of present paper

The purpose of this paper is to suggest a scheme whereby the quantitative food intake of the first couple of weeks of life can be regulated or checked, to show how the scheme has worked out in practice for babies of different birth-weights, and to indicate its limitations. The differential diagnosis in the neonatal period between underfeeding and overfeeding on the breast is often uncertain, unless it is possible by test-feeding or expression of feeds to estimate

the food intake and to compare this with the calculated need. At the same time there are in practice so many unknown factors that any quantitative scheme can only be used as a guide and not as a hard-and-fast system of feeding, and the final criterion of a baby's quantitative needs must always be his progress, including his rate of gain in weight.

The calorie value of colostrum and human milk in the first weeks of lactation

One of the biggest unknown factors in the feeding of new-born babies is the actual calorie value of the colostrum and early milk of the individual mother on any one day. Statements of the 'average' calorie value of colostrum are sometimes misleading when dealing with an individual baby, unless it is remembered that these values vary considerably. The variations in composition are greatest in the first few days. According to Langstein, Rott and Edelstein (1913) the calorie value of colostrum obtained immediately after birth may be double that of mature milk. It is highest when the secretion of the breasts is thick and yellow. Nevertheless, in spite of such extremes, average calorie values do furnish a good working basis for feeding most babies.

Table 1 gives some typical analyses of colostrum and early breast milk published by different authors. In the secretion obtained from the breasts in the first few days of life, protein is high, and sugar (and probably also fat) are low, as compared with the percentages in milk after lactation is fully established. The composition changes rapidly during the first week of life. Individual variations are illustrated by the figures of Widdows and her co-workers (1935).

TABLE 1
COMPOSITION AND CALORIE VALUE OF COLOSTRUM AND EARLY BREAST MILK

PERIOD AFTER PARTURITION	COMPOSITION PER CENT.			CALORIES PER FLUID OZ. (CALCULATED FROM PREVIOUS COLUMNS)	AUTHORS AND DATE
	PROTEIN	SUGAR	FAT		
1st day: Average	7·86 (11)	3·17 (14)	—	—	Widdows, Lowenfeld, Bond, Shiskin and Taylor, 1935.
Range ..	2·64–14·1	1·08–6·26			
3rd day: Average	2·80 (27)	6·32 (37)	—	—	Same
Range ..	1·36–8·67	3·55–7·77			
5th day: Average	1·70 (20)	6·94 (28)	—	—	Same
Range ..	1·27–2·34	4·77–7·87			
1st to 3rd days..	4·35 (30)	5·34 (30)	2·07 (3)	16·8 (3–30)	Widdows, Lowenfeld, Bond and Taylor, 1930. Widdows and Lowenfeld, 1933.
8th to 13th days	1·45 (26)	6·35 (46)	4·34 (11)	20·7 (11–46)	Same
1st to 13th days	2·39 (108)	5·84 (115)	3·53 (24)	18·9 (24–115)	Same
3rd day.. ..	3·52 (8)	5·43 (8)	4·34 (8)	21·9 (8)	Hammett, 1917.
5th day.. ..	1·74 (8)	6·08 (8)	2·88 (8)	17·3 (8)	Same
3rd to 11th days	2·00 (40)	6·09 (40)	3·62 (40)	18·9 (40)	Same
3rd to 12th days	2·25 (5)	7·59 (5)	3·15 (5)	18·7 (5)	Holt, Courtney and Fales, 1915.
1–9 months ..	1·15 (17)	7·50 (17)	3·26 (17)	18·4 (17)	Same

The number of estimations on which each average is based is shown by the figure or figures in brackets. Holt, Courtney and Fales' figures are based on individual 24-hour samples and pooled composite samples.

They found that on the first day the protein varied between 2·64 per cent. and 14·1 per cent., and the sugar between 1·08 per cent. and 6·26 per cent. Moreover, the drop in protein content occurred more rapidly in multiparae than in primiparae, and a sudden increase in the volume secreted by the breasts may be accompanied by a large drop in fat percentage, and consequently in calorie value. The calorie values shown in table 1 are calculated from data in the articles quoted. The low calorie value inserted for the first to third days, 16·8 calories per fluid oz., must be taken with caution; the authors quoted (Widdows and Lowenfeld, 1933) themselves give no average values for fat for these days, and the low fat percentage, and consequent low calorie value, here tentatively given, is based on only three analyses for fat. The greatest variability in composition occurs in the first three to four days of life when the volume secreted is small, consequently the calorie value of this early and rather scanty secretion would play only a small part in determining the calorie value of the composite secretion of the first ten days. For example, in the series, analysed below, of breast-fed babies who regained their birth weight by ten days old (see table 2), the volume sucked in the first three days of life was only 9·5 per cent. of that of the next seven days, and if the calorie value per oz. of fluid for the first three days were as much as 30 (certainly too high a figure), and for the next seven days was 20, the average for the whole intake of the ten days would be only 21. For the first two weeks of life, the average calorie values per fluid oz., based on the average composition of series of samples taken by different authors are surprisingly similar [see table 1: Widdows et al. (1930 and 1933) first to thirteenth day; Hammett (1917) third to eleventh day; and Holt et al. (1915) third to twelfth day respectively]. Neglecting decimals, the value is 19, i.e. about the average of human milk after lactation is fully established.

For convenience, the round number 20 is generally taken as the calorie value of human milk. From the figures here given, it therefore seems legitimate for practical purposes (and the aim of this paper is essentially practical), to use the same round number as representing the average calorie value of the secretion of the breasts in the first two weeks after parturition. By reckoning the calorie value as 20 instead of 19 per oz. about 5 per cent. is added to the calorie value, but an error of this grade in average values is relatively unimportant when the measure of intake is also subject to error, and calorie values are known to vary.

The calorie concentration of artificial feeds employed

All artificial feeds used by the author in the feeding of new-born babies have been made up to provide approximately 20 calories per fluid oz. Dilute feeds have not been used. Artificial feeds given to babies in the present investigation, can therefore be assumed to have a calorie value approximately the same as that of breast milk.

Formula for the calculation of food requirements

The scheme here suggested may not be original, though the present author has not come across it elsewhere. The scheme is empirical. It is an attempt to

reduce to an easily remembered formula the food intake on which most babies will make satisfactory progress during the first two weeks of life. The scheme assumes that the average value of human colostrum and milk during the first two weeks is 20 calories to each fluid oz., and that by the seventh day of life (i.e. at six days old), and for the following week the baby requires 50 calories per lb. of his birth-weight. The calorie requirement of the seventh day is divided by seven, and to give a steady rate of increase in food in the first week the scheme assumes that, starting from one-seventh on the first day, the baby requires an increase of one-seventh each day, or, calling the birth weight x lb., say $\frac{1}{7} \times 50x$ calories. Thus if the baby weighs 7 lb. at birth, the calorie intake on the seventh day (six days old) would be 50×7 or 350 calories; on the first day he would receive $\frac{350}{7}$ or 50 calories, with an increase of 50 calories each day till six days old. Since most mothers have little secretion in the breasts till the third day after parturition, it is obvious that this scheme overestimates the normal baby's food intake from the breast for the first two days. Moreover, since in the following tables (see tables 2 and 6) the intake is reckoned from midnight to midnight, the ' first day ' might be any period under twenty-four hours, and would average say twelve hours. If a baby has to be hand-fed from the outset, then feeding on the basis of this table can be started on the first day, provided breast milk is available; if the baby is artificially fed the rate of increase must often be rather slower, especially in the first four days; certainly if there is any tendency to vomit or the baby's abdomen is distended a more gradual increase is indicated, perhaps reaching 50 calories per lb. birth-weight about the tenth day of life.

According to the formula a baby would receive within the whole of the first week of life 4×50 calories per lb. birth-weight, and within the first ten days 7×50 calories per lb. birth-weight. This amounts to an average of 29 calories per lb. per day for the first seven days, 31 calories per lb. per day for the first eight days, or 35 calories per lb. per day for the first ten days. These figures are 30 per cent. to 52 per cent. higher than those of von Reuss, depending on whether the intake for eight days or ten days is considered.

The actual food intake of twenty consecutive breast-fed babies at the Mothers' Hospital compared with their requirements according to the formula

Table 2 shows the daily food intake (calculated in calories) for the first ten days of life of twenty consecutive babies who were entirely breast-fed. All but two twins were over $5\frac{1}{2}$ lb. at birth. All the mothers were in one ward at the Mothers' Hospital, Clapton, London; three were married and the rest were unmarried mothers; fourteen were primiparae. The babies were fed either six or five times daily and were weighed before and after each feed for the first ten days of life. The volume of feeds was recorded to the nearest quarter-ounce, reckoning one-ounce increase in weight as representing one fluid ounce of milk. With small volumes of milk, weighing only to the nearest quarter-ounce may introduce a large percentage error. If a baby did not suck well the breast was sometimes emptied and the milk given by hand. In the table the babies are divided into three groups, according to their weight at ten days old:

i.e. those over birth-weight, at birth-weight, and under birth-weight. For the whole of the first ten days (on the assumption that the calorie value of the milk was 20 per ounce), it was found that the intake of those babies who more than regained their birth-weight averaged 93 per cent. of the formula requirements; those at birth weight 88 per cent.; and those under birth-weight (average three ounces under birth-weight) 73 per cent. Presumably the intake in the first two days would have been rather larger if the series had included a larger proportion of babies of multiparae. If the period two to six days old (i.e. the first week with the exclusion of the first two days when there is little secretion of milk) is taken, the figures for the three groups are 101 per cent., 93 per cent. and 72 per cent. respectively. Combining the first two groups, the average for all babies at or above their birth weight by ten days old is 99 per cent. So the average actually taken over this period by breast-fed babies progressing satisfactorily closely approximated to the formula.

So far the average total intake as compared with the formula has been considered. The average daily intake for each day after the first two is also not very different from the schedule. Taking all the babies who regained their birth-weight by ten days old, the average calorie intake on any one day from the third to the tenth day of life was within 12 per cent. of that required by the formula.

Turning from group averages to individuals it is found, of course, that the intake of individual babies varies widely. In the first ten days the babies over birth-weight by ten days old took anything between 69 per cent. and 122 per cent. of the quantity required by the formula, and those at birth-weight between 72 per cent. and 103 per cent., i.e. the intake of babies making satisfactory progress might be as much as 31 per cent. under the formula figure (assuming always that the calorie value of the milk was 20 per fluid ounce). Nevertheless, from two to six days old, and also from seven to nine days old, more than two-thirds of the babies took over 85 per cent. of their formula requirements. Probably, those babies who gained well on a smaller volumetric intake, were actually getting milk of a higher calorie value than the average, and their calorie intake has been underestimated as a result. After ten days old the number of babies weighed before and after all feeds was too small to be worth quoting.

The fluid intake of these babies was augmented during the first week; they were usually given some water between feeds during the first three to five days of life, sometimes for longer, but the total amount of water given was not large, say, half to four ounces in the day. None of these babies suffered from inanition fever. Their average loss in weight in the first few days was 5·1 oz. or about 4·5 per cent. of birth weight.

The food intake of other groups of full-term babies compared with the formula requirement

In order further to check the utility of the formula for feeding full-term babies, the intake of other groups of infants is given in table 3 in terms of the formula requirement.

TABLE 2

CALORIE INTAKE IN THE FIRST TEN DAYS OF LIFE OF TWENTY CONSECUTIVE BREAST-FED BABIES AT THE MOTHERS' HOSPITAL

Calorie value of 1 fluid ounce of breast milk or colostrum reckoned as 20 Formula figures calculated to nearest quarter pound

WEIGHT AT 10 DAYS	PARITY OF MOTHER	BIRTH WEIGHT LB. OZ.	LOSS OR GAIN IN OZ.			CALORIE INTAKE ON EACH OF FIRST 10 DAYS OF LIFE: AGE IN DAYS										INTAKE AS PER CENT OF FORMULA FIGURES: AGE IN DAYS		
			MAX.	AT 7 DAYS	AT 10 DAYS	0	1	2	3	4	5	6	7	8	9	0–9	2–6	7–9
Over birth weight ..	M	6 5	$-3\frac{1}{2}$	$+3\frac{1}{2}$	$+7\frac{1}{2}$	* 0	50	130	300	350	360	330	400	360	380	**122**	**132**	**122**
	M	5 12	$-\frac{1}{2}$	$+8\frac{1}{2}$	+7	30	60	190	290	310	290	270	310	290	300	**111**	**132**	**105**
	P	8 4	-3	$+4\frac{1}{2}$	+5	0	90	150	300	360	380	380	370	370	360	**96**	**107**	**89**
	M	6 11	-8	-1	+4	0	80	120	170	170	280	300	250	250	320	**82**	**87**	**81**
	P	6 15	$-1\frac{1}{2}$	+1	+4	0	50	130	190	230	270	320	290	330	310	**87**	**91**	**89**
	P	7 5	-6	$+\frac{1}{2}$	+4	0	0	110	210	290	280	280	330	320	320	**84**	**91**	**89**
	P	5 7	-6	$-2\frac{1}{2}$	$+1\frac{1}{2}$	0	20	60	100	130	160	210	180	230	240	**69**	**67**	**79**
	P	6 3	$-3\frac{1}{2}$	$-1\frac{1}{2}$	$+1\frac{1}{2}$	0	40	130	180	260	310	300	350	340	280	**100**	**106**	**104**
	P	7 5	$-8\frac{1}{2}$	+0	+1	0	30	130	260	320	370	400	410	400	430	**109**	**115**	**114**
	M	9 10	-8	$+\frac{1}{2}$	+1	0	30	140	240	320	330	330	360	370	380	**75**	**80**	**78**
	Average:	6 $15\frac{1}{2}$	$-4{\cdot}85$	$+1{\cdot}35$	$+3{\cdot}65$	3	45	129	224	274	303	312	325	326	332	**93**	**101**	**95**
At birth weight ..	P	6 0	$-5\frac{1}{2}$	-1	+0	0	30	90	180	160	240	230	260	240	230	**79**	**84**	**81**
	P	6 10	$-6\frac{1}{2}$	$-4\frac{1}{2}$	+0	0	0	30	90	100	180	280	290	310	360	**72**	**59**	**99**
	P	7 2	$-5\frac{1}{2}$	-1	+0	0	150	270	270	320	280	330	280	330	305	**103**	**118**	**87**
	M	8 1	-5	$-\frac{1}{2}$	+0	0	110	270	280	350	340	340	350	410	350	**100**	**111**	**93**
	Average:	6 $15\frac{1}{4}$	$-5{\cdot}50$	$-1{\cdot}75$	+0	0	72	165	205	232	260	295	295	322	311	**88**	**93**	**90**
Over or at birth weight (combined)	Average:	6 $15\frac{1}{2}$	$-5{\cdot}1$	$+0{\cdot}5$	$+2{\cdot}6$	2	53	139	219	262	291	307	316	325	326	**92**	**99**	**93**
	As per cent. of formula figures ..					**4**	**53**	**93**	**109**	**105**	**97**	**88**	**90**	**93**	**93**			
Under birth weight..	M	7 0	-7	$-2\frac{1}{2}$	-1	0	0	70	120	240	310	270	260	350	300	**78**	**81**	**87**
	P	5 5	-8	-5	$-1\frac{1}{2}$	0	20	60	120	100	130	190	140	220	230	**66**	**64**	**75**
	P	6 0	$-7\frac{1}{2}$	-4	$-2\frac{1}{2}$	0	60	70	90	130	230	280	260	270	300	**80**	**75**	**92**
	P	6 5	$-8\frac{1}{2}$	-5	$-2\frac{1}{2}$	0	30	90	140	200	260	280	300	250	310	**85**	**87**	**92**
	P	9 3	-11	-8	-3	0	0	70	100	150	200	260	290	270	330	**52**	**47**	**64**
	P	6 8	-12	-7	$-7\frac{1}{2}$	0	60	100	150	180	280	230	260	270	270	**79**	**81**	**82**
	Average:	6 $11\frac{1}{2}$	$-9{\cdot}0$	$-5{\cdot}25$	$-3{\cdot}0$	0	28	77	120	167	235	252	252	272	290	**73**	**72**	**82**
	As per cent. of formula figures ..					**0**	**29**	**53**	**63**	**70**	**81**	**75**	**75**	**81**	**86**			

* This column shows intake from birth to midnight, an average of, say, 12 hours.

TABLE 3

CALORIE INTAKE OF GROUPS OF FULL-TERM BABIES IN THE FIRST TEN DAYS OF LIFE

100 c.c. breast milk reckoned as 70 calories, i.e. approximately 20 calories per fluid oz.

AUTHOR AND YEAR	NO. OF BABIES AND FEEDING	BIRTH-WEIGHT	PROGRESS	AVERAGE CALORIE INTAKE ON EACH OF FIRST 10 DAYS OF LIFE: AGE IN DAYS										INTAKE AS PER CENT. OF FORMULA FIGURES: AGE IN DAYS		
				0	1	2	3	4	5	6	7	8	9	0–9	2–6	7–9
Feer (1902) ..	10 Breast only	7 lb. 12¼ oz.	At 13 days old nearly 2 oz. over average birth-weight	3	35	124	220	319	384	386	397	393	422	**99**	**104**	**104**
			Per cent. of formula fig.	**5**	**32**	**75**	**100**	**116**	**116**	**100**	**103**	**102**	**109**			
Faber (1922)..	179—64 Breast and supplement	7 lb. 6 oz.	Average birth-weight regained at 7 days old	73	152	220	286	317	338	360	363	356	368	**108**	**114**	**97**
			Per cent. of formula fig.	**135**	**142**	**137**	**134**	**119**	**105**	**96**	**97**	**95**	**98**			
Opitz (1911) ..	75 Breast and presumably supplement	3·0–3·5 kilo. Average taken as 7 lb. 2½ oz.	Birth-weight regained at 8 days old	40	138	208	260	302	324	319	340	327	* 334	**102**	**109**	**92**
			Per cent. of formula fig.	**77**	**134**	**134**	**126**	**117**	**104**	**88**	**94**	**90**	**92**			

The calorie values here given do not always correspond with the calorie values as reckoned in the papers quoted, because they have been re-calculated on the basis of one fluid oz. of breast milk supplying 20 calories, in order that the figures in this table may be comparable with figures in the rest of this paper.

* Opitz does not give the intake at nine days old: this figure is the average of the intake of the two previous days.

Feer (1902) gives the quantity of breast milk taken by ten babies who averaged 7 lb. 12 oz. at birth. By thirteen days old they averaged nearly two ounces over birth-weight, so they probably regained their birth-weight by about ten days old. For the first three days, i.e. before the milk came in, they took less than the formula requirement, and thereafter slightly more than this estimate, so that the intake for the first ten days was almost exactly that required by the formula. Faber's (1922) babies, who were supplemented from the first day with as much food as they would take from a bottle, took well over the formula requirement in the first five days, and from the sixth day rather less, so that they averaged 8 per cent. over the formula figures for the first ten days. Opitz's (1911) cases show the same sort of tendency as Faber's, and presumably received supplements in the first few days of life; within the first ten days they took almost exactly the formula requirement.

Hence, judged by these three series, as well as by the author's own series, the formula approximated fairly closely to the quantity of food taken by groups of babies who made normal progress. The calorie intake for each of these groups has been calculated (or re-calculated) on the basis of 20 calories per fluid ounce in order to compare them with the author's own cases, so that the calculated calorie intake here shown does not always tally with that of the authors themselves. It would seem that if a baby is given fairly liberal feeds in the first two or three days, he will probably take rather less than the average in the latter part of the first ten days.

The progress made by 107 consecutive premature babies at the Mother's Hospital whose feeding was guided by the formula

For a number of years this formula has been used as a guide in feeding premature and immature babies at the Mothers' Hospital, Clapton, a maternity hospital of one hundred beds. Table 4 sets forth the average gain in weight

TABLE 4

PREMATURE BABIES WHOSE FEEDS WERE ADJUSTED BY THE FORMULA: AVERAGE WEIGHTS TO SHOW THE BABIES' PROGRESS

All babies, born in the Mothers' Hospital between July 1938 and June 1939, who weighed 5½ lb. and less at birth

GROUP BY BIRTH WEIGHT	NUMBER		BABIES SURVIVING AT 10 DAYS OLD			
	BORN	SURVIVING AT 10 DAYS	AVERAGE BIRTH-WEIGHT. LB. OZ.	LOSS IN WEIGHT		AVERAGE GAIN AT 10 DAYS OLD IN OZ.
				AVERAGE IN OZ.	PER CENT. BIRTH-WEIGHT	
2½ lb. to 4 lb.	14	8	3 10·3	−1·81	3·1	+2·56
Over 4 lb. to 4½ lb. ..	12	10	4 4·4	−3·20	4·7	+1·00
Over 4½ lb. to 5 lb. ..	35	33	4 12·9	−3·54	4·6	+0·44
Over 5 lb. to 5½ lb. ..	57	56	5 5·2	−4·04	4·7	+1·21
2½ lb. to 5½ lb. (combined)	118	107	4 15·0	−3·64	4·6	+1·07

of all the babies of 5½ lb. and less born in the twelve months from July 1, 1938, to June 30, 1939, and shows that the progress of these immature babies was on

the whole good. One hundred and eighteen such babies were born; of these, one hundred and seven were surviving at ten days old. At that age they averaged approximately one ounce over birth-weight. Their average loss in weight after birth was just over three and a half ounces, or about 4·5 per cent. of birth-weight. The babies are subdivided by birth-weight, and for each subdivision the initial loss in weight is less than 4·75 per cent. of birth-weight. So that as regards these babies the use of the formula was justified by results.

The calorie intake of 43 premature babies and their progress

Though the formula was used as a guide or check in the feeding of all the premature babies, complete records of food intake were only kept in a certain number of cases. Of these hundred and seven premature babies, complete feeding records up to ten days old were kept in thirty-five cases, and up to seven days old in forty-three cases. The babies for whom the records were incomplete were nearly all the stronger and more vigorous babies, who were able at an early stage to suck direct from the breast, so that the forty-three babies whose records are available (see tables 5 and 6) included nearly all the smallest babies and the

TABLE 5

THE CALORIE INTAKE OF 43 PREMATURE BABIES IN THE FIRST TEN DAYS OF LIFE, AND THEIR PROGRESS: BABIES INCLUDED IN TABLES 4 AND 6

GROUP BY BIRTH-WEIGHT	AVERAGE BIRTH-WEIGHT LB.	AVERAGE BIRTH-WEIGHT OZ.	NO.	INITIAL LOSS IN WEIGHT: AVERAGE IN OZ.	INITIAL LOSS IN WEIGHT: PER CENT. BIRTH-WEIGHT	AVERAGE LOSS OR GAIN IN OZ.: AT 7 DAYS	AVERAGE LOSS OR GAIN IN OZ.: AT 10 DAYS	INTAKE AS PER CENT OF FORMULA REQUIREMENT: 0–6 DAYS OLD	INTAKE AS PER CENT OF FORMULA REQUIREMENT: 0–9 DAYS OLD
2½ lb. to 4 lb. ..	3	10	7	−2·29	4·7	−0·79	+1·93(7)	**97**	**101 (7)**
Over 4 lb. to 5 lb.	4	10½	28	−3·89	5·2	−1·71	+0·01 (22)	**88**	**93 (22)**
Over 5 lb. to 5½ lb.	5	4¼	8	−4·81	6·0	−2·28	+0·33(6)	**85**	**88 (6)**
2½ lb. to 5½ lb. (combined) ..	4	10·0	43	−3·80	5·1	−1·67	+0·44 (35)	**89**	**94 (35)**

Figures in brackets show number of cases at 10 days old.

feeble babies. Thus, while they included fourteen out of eighteen babies weighing 2½ to 4½ lb., they included only twenty-nine out of eighty-nine babies weighing 4½ to 5½ lb. The food intake for the whole group for whom figures are available was 94 per cent. of the calculated requirement for the first ten days; for those of 4 lb. and less it was 101 per cent., for those of 4 to 5 lb., 93 per cent., and for those of 5 to 5½ lb., 88 per cent. This relatively higher feeding of the smallest babies probably reflects the attitude of the nursing staff: in the case of very small babies it is recognized that they cannot take all their milk directly from the breast and that it is of importance that they should not be underfed, consequently their intake averaged almost exactly that laid down in the schedule, and by ten days old they were approximately two ounces over

birth-weight. With bigger and stronger babies it was felt that more liberties could be taken, and in an effort to get the baby to suck from the breast, the nurses might omit to give him quite as high a feed, so that the progress of the larger babies tended to be a little slower, and they averaged almost exactly birth-weight at ten days. The average daily intake is shown in table 6. Taking the whole group of forty-three babies the average intake on the first day of life was 36 per cent. of the schedule requirement (assuming that the average period from birth to midnight was only twelve hours it would be raised to 72 per cent.), and after two days old it was always within 4 per cent. of the schedule figure. The average loss in weight after birth was 3·8 oz., or 5·1 per cent. of birth-weight (see table 5), so that these forty-three babies gained only a little more slowly than the whole group of a hundred and seven premature babies, in spite of the fact that they included nearly all the feeble babies.

The two babies in the series whose percentage intake for the first ten days was smallest were two 5 lb. babies who took respectively 61 per cent. and 60 per cent. of the schedule requirement, and were half an ounce and three and a half ounces under birth-weight at ten days old. Both were ill, one had blue asphyxia, some bleeding from the nose, a shrill cry and subnormal temperature (probably haemorrhagic disease with some intra-cranial bleeding), the other had loose stools and convulsive twitchings on the seventh and eighth days of life. Of the rest of the series of forty-three, five had cyanotic attacks, nine had body temperatures of 95° F. or lower, one melaena, one a cephalhaematoma, and three vomited, so that the fact that at ten days old the average weight of the whole group was just over birth-weight must be considered satisfactory.

After the baby reached an intake of 50 calories per lb. birth-weight, subsequent increases were dependent on his appetite and on his rate of gain in weight. About 50 calories per pound birth-weight was aimed at during the second week of life until the baby showed signs of desiring more, or failed to gain adequately. The average daily intake for the second week for the twenty-six premature babies in the series for whom details are available (see table 6) was 53 calories per pound birth-weight, and the average gain for the week 5·4 oz. The intake for individual babies usually exceeded 45 calories per pound birth-weight; the highest in the group was 66 calories. After the end of the second week, a further rise in calorie intake was usually necessary.

The human milk given to the smaller premature babies in the first week was often derived from mothers in the second week of lactation, and its calorie value was therefore probably more constant than that of colostrum. When human milk was not available, sweetened condensed milk in a dilution of one in five by volume (providing approximately 20 calories per fluid oz.) was usually given, but this was seldom necessary for the smaller premature babies in the first two weeks.

During the first two to five days of life premature babies were given water between feeds in about the same volume as that taken in the feeds. Thereafter the volume of the feeds exceeded that of the plain water, and by the second week of life most babies received only one to two ounces of extra water daily, though if the baby seemed thirsty he was given more, and occasionally a baby took five or six ounces in the day.

TABLE 6

CALORIE INTAKES OF PREMATURE BABIES IN THE FIRST AND SECOND WEEKS OF LIFE: BABIES INCLUDED IN TABLES 4 AND 5

	FIRST WEEK OF LIFE									SECOND WEEK OF LIFE			
	AVERAGE BIRTH-WEIGHT LB. OZ.	NO.	AVERAGE CALORIE INTAKE ON EACH OF FIRST 7 DAYS OF LIFE							AVERAGE TOTAL IN 0–6 DAYS, I.E. IN 1ST WEEK	NO.	AVERAGE DAILY INTAKE, 7–13 DAYS OLD	AVERAGE PER LB.	AVERAGE GAIN 2ND WEEK
			0	1	2	3	4	5	6					
Intake	4 10·0	43	12*	52	85	125	158	179	205	819 calories	26	228 calories	53 calories	+5·4 oz.
Formula requirement ..	4 10·0	—	33†	66	99	132	165	198	231	924 calories				
Intake as per cent. of formula requirement			**36**	**79**	**86**	**95**	**96**	**90**	**89**	**89**		**106**		

* This figure is the intake from birth till midnight, probably an average of 12 hours.
† This figure is the calculated requirement for 24 hours.

Test feeds: first and last feeds of the day compared with the rest

In most maternity hospitals in this country the amount of work to be got through by the nurses places a limit on the number of test feeds which can be carried out, particularly by the night staff. Hence it is desirable to know what guidance can be obtained as to the total intake from test feeds carried out by the day staff when, as is usual, the quantity taken at the first and last feeds of the day is unknown. For twenty-five babies the average volume of first and last feeds has been compared with the average volume of the rest of the feeds of the day, either five or six feeds being given in twenty-four hours. Complete records were available for eighty-eight days during which 513 feeds were given; the majority of complete records were for the first week of life. If the average of each of the three or four feeds given during the day-duty period is called 100, the average of the first and last feed came to 110 each. It must be remembered moreover, that intake was estimated only to the nearest quarter ounce. This 10 per cent. difference, if significant, would mean that if the total intake for twenty-four hours for a group of babies were reckoned on the average of the day-time feeds, the result would be too low by 4 per cent. if five feeds are given, and by 3·3 per cent. if six feeds are given, differences that are sufficiently small to make the average of the day feeds a satisfactory guide. Unfortunately, however, the individual variations are large, so that for one baby in a single day the error sometimes may be considerable. Moreover, the mother's milk supply will be affected by circumstances, such as interrupted sleep at night or an emotional upset in the day.

Discussion

Considerations governing the giving of supplements. The start given the baby in the first fortnight of life plays a large part in his progress for the next few months. Very many of the 'feeding difficulties' of infancy originate in mismanaged feeding during the early weeks. As already stated, this formula for calculating a baby's requirements should not be adhered to rigidly, but should simply be used as a guide. The sixty-three babies, full term and premature, at the Mother's Hospital, whose records are analysed in this paper, include seven getting about 20 to 30 per cent. under the formula requirement for the first ten days, who nevertheless made normal progress. The probable explanation is that the calorie value of the breast milk they received was higher than the average, so that their actual calorie intake was greater than that calculated. Four babies received 10 per cent. or more above the schedule requirement in the first ten days, and these averaged six ounces over their birth-weight at ten days old.

In deciding whether an individual baby, whose gain is inadequate, should have a supplement, various factors should be taken into consideration besides the actual volume intake, and the problem is often complicated by other factors. A baby getting insufficient food may become or remain lethargic, and suck badly; if given a supplement, he may suck better. On the other hand, a baby given too liberal a supplement may simply go to sleep when put to the breast. The psychological effect on the mother is also important, and some psychological insight is necessary to arrive at a right decision. For example,

a mother's worry over her baby's failure to gain may result in a poor milk secretion, or, on the other hand, some mothers finding that their babies are gaining well on breast-milk and supplement conclude there is no good reason for persevering in breast feeding. When ordering supplements, information is always needed, not only as to the amount taken in test feeds, but also as to the amount of milk, if any, remaining in the breasts, as to the baby's behaviour during the feed, as to the mother's management of the feed and her attitude to the problem of feeding. Much of this work in a maternity hospital must devolve on the ward sister, and balanced judgment and skilled handling on her part are essential if good results are to be obtained. Speaking generally, if the mother's stay in hospital can be extended, supplements can often be withheld, and lactation may increase satisfactorily, whereas if the baby is underfed and has to be discharged early it is safer to supplement before discharge. To send out babies wholly on the breast, but underfed, is to court trouble for mother and baby, and is probably the commonest reason for breast-feeding being abandoned.

Every paediatrician and medical officer in charge of a welfare centre is familiar with the common remark that the mother's milk failed after her discharge from the maternity hospital, and the baby was consequently wholly bottle-fed. Those who have the opportunity of tracing the past history, find time and again that in such cases the mother's lactation before discharge was inadequate, and the baby underfed, so that it is scarcely surprising if the mother, deprived of the help she might have been given in hospital, is unable to cope alone with the often difficult task of adjusting the baby's feeds satisfactorily. Parents and hospital authorities, therefore, need to realize that inadequate lactation often necessitates a longer stay in hospital in the interests of the baby. If this cannot be achieved, as must often happen in the present time of war, the supplements on discharge should be fully adequate, and the mother's co-operation should be sought in reducing the supplements as and when possible, and she should be told that subsequent omission is very often possible. Brennemann (1938) has lent the weight of his authority to the claim of the new-born baby to be given enough food, and states boldly, 'The new-born baby that is on the breast alone, that is not vomiting and has no diarrhoea and is not gaining in weight after the third day of life, is not getting enough to eat and should be given more.'

Overfeeding. The formula for the calculation of feeds has also its uses in picking out the baby that is taking too much from the breast and vomiting or having loose stools as a result. The chief risk of overfeeding is, however, to the hand-fed baby, and the use of a formula should prevent sudden increases in food as well as the giving of excessive quantities: always remembering that caution is needed in giving the full schedule requirement if breast milk is not available.

The influence of feeding on the neonatal death rate. In the Registrar's General's Statistical Review for the year 1936, the infant mortality per 1000 live births during the years 1906 to 1910 is compared with that of 1936, about thirty years later. In this country in that period the mortality of infants under twenty-four hours old had dropped by only 7 per cent., of those one to fourteen days by 22 per cent., whereas that of infants aged fourteen days to twelve

months old had fallen by 62 per cent. It is generally accepted that among the many factors at work, improved feeding has played an important part in bringing down the death rate of infants over fourteen days old to a little over one-third of the old figure; but improvement in feeding cannot be expected to lessen materially the death rate in the first twenty-four hours of life. What of the next thirteen days? Better feeding will not save the lives of babies dying as the result of gross malformations or gross trauma, but what of the premature babies and twins, the babies ill with infections, the babies of mothers with poor lactation, the babies who, for one reason or another, have to be fed by hand in the early weeks? Many such are potentially healthy children. Though feeding difficulties do not figure in the death certificate, there is no doubt that they contribute to death in many instances, and that the neonatal death rate could be materially lowered by better feeding. And just as knowledge of how to calculate quantitative needs has vastly improved the feeding of older babies, so it should help in the feeding of the new born.

Summary

The day-to-day calorie needs of new-born babies is a subject which has been much neglected and about which text books provide the most diverse statements. In this paper the calorie value of colostrum and early human milk is discussed. Its value is taken in the author's calculations as 20 per fluid ounce.

A formula is suggested whereby the food intake of new-born babies may be regulated. According to this the baby should receive on the first day of life calories equivalent to $\frac{1}{7} \times 50 \times$ birth-weight in pounds, and his feeds should increase by this same amount each day of the first week, so that by the seventh day of life he would be given 50 calories per pound birth-weight. It is pointed out that the formula over-estimates the intake of normal breast-fed babies during the first two days when breast secretion is scanty. In the second week of life 50 calories per lb. birth-weight was taken as the usual requirement. The importance is emphasized of using these figures simply as guides and not to enforce a rigid system of feeding.

The calorie intake of twenty healthy breast-fed babies at the Mother's Hospital, Clapton, has been compared with the quantities calculated from this formula. The average intake on any one day after the first two days of life, of those who regained their birth-weight by ten days old, was found to be within 3 to 12 per cent. of the schedule. Three other series of full-term babies making good progress, whose average food intake for the first ten days has been recorded by different workers, received in these ten days a total quantity within 1 to 8 per cent. of the formula requirement: those who took larger quantities in the first days of life tended to take less than others in the latter part of the first ten days, and vice versa.

Calculations from test feeds on twenty-five full-term babies showed that estimates of total intake based on the feeds given during the duty-periods of the day staff gave, on the whole, a fairly accurate figure for the twenty-four-hour intake, hence three or four test feeds in the twenty-four hours should generally provide an adequate check on a baby's intake.

One hundred and seven consecutive premature babies at the Mother's Hospital who had their food intake checked and guided by the formula, made good progress and averaged one ounce over their birth-weight at ten days old.

For a group of forty-three premature babies in this series complete figures are available. Their birth-weights varied between 2½ lb. and 5½ lb., and their intake for the first ten days was within 6 per cent. of that allowed by the formula. During the second week of life, the intake averaged 53 calories per pound birth-weight per day, i.e. again within 6 per cent. of the formula requirement.

All artificial feeds were given in a strength to provide approximately 20 calories per fluid ounce. Dilute feeds were not given. The fluid intake was augmented by giving water to full-term babies during the first three to five days of life or longer, to premature babies generally during the first fourteen days. Premature babies during the first two to five days received water between feeds in about the same volume as provided in their feeds.

It is hoped that wide adoption of a scheme for calculating the approximate calorie needs of new-born babies would bring about a fall in the neonatal death rate, as well as improved health in the subsequent months, by contributing to better management in the most critical period of life.

The author is much indebted to Sisters and nurses at the Mothers' Hospital for their generous help, and for the extra work they have given to enable this investigation to be carried out. The credit when good results are obtained with premature babies in hospital must always belong primarily to those who undertake the skilled and exacting work of nursing. To the resident medical staff who have shared with the author the medical care of the infants and supervision of feeds, she tenders sincere thanks for their constant co-operation.

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A COMPARISON OF THE VALUE OF CRYSTALLOID SOLUTIONS, WHOLE BLOOD AND BLOOD PLASMA IN THE TREATMENT OF DEHYDRATION IN INFANCY *

BY

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In an earlier communication (Aldridge, 1941) attention was drawn to the fact that in addition to water loss in dehydration in infancy, there is loss of electrolytes which may alter the acid base balance of the blood, and that oliguria may play a part in producing the condition. Treatment of dehydration is, therefore, designed to deal with these three factors; to this end fluid in excess of normal requirements (at least 2½ ounces per pound of body weight per day) must be administered, and if, as is usually the case, the patient does not take sufficient fluid by mouth, it must be given parenterally.

The common methods of administering fluid parenterally are the subcutaneous, intraperitoneal and intravenous routes. At the Birmingham Children's Hospital the subcutaneous and intravenous routes are used almost exclusively. The fluids used are normal (0·9 per cent.) saline solution and 5 to 10 per cent. solutions of glucose in sterile triply distilled water or in normal saline. Moderate degrees of dehydration are treated by giving normal saline as a continuous drip subcutaneously into the thigh, using between 100 and 150 c.c. (10 to 15 c.c. per pound of body weight). In children showing severe dehydration fluid, usually 5 or 10 per cent. glucose in saline, is given intravenously either in single doses of from 10 to 15 c.c. per pound of body weight or by continuous drip which is kept running for twenty-four, forty-eight or even seventy-two hours, depending on the condition of the patient. Although it has been the custom to give citrated blood to patients who do not respond to such treatment, the desirability of so doing is discussed in detail later in the paper.

PARENTERAL INJECTION OF CRYSTALLOID SOLUTIONS IN DEHYDRATION

Various authorities have advocated that these solutions should be given by combinations of the subcutaneous, intraperitoneal and intravenous routes, and

* Part of a thesis submitted for the degree of M.D., of the University of Cambridge.

claims have also been made for the particular efficacy of solutions which contain bicarbonate, lactate, calcium and other substances. The use of fluids such as Hartmann's lactate-Ringer solution has been strongly recommended but this has not been used extensively at the Birmingham Children's Hospital. The impairment of renal function can only be relieved by an adequate intake of fluid, and the use of hypertonic glucose (10 per cent.) intravenously is almost universally commended as a diuretic. Notwithstanding the importance of treating renal impairment, it is a matter of urgency to replenish the fluid which has been lost and it must not be forgotten that the prolonged administration of any hypertonic solution intravenously may, through its diuretic action, actually increase dehydration. For this reason most observers advise the use of normal saline subcutaneously in conjunction with 10 per cent. glucose intravenously especially because glucose is said to aid absorption of saline.

The various methods advised for the treatment of the dehydration of infantile gastro-enteritis aim at replacing those substances, such as water and salts, which have been lost as the result of diarrhoea and vomiting. Many writers have stated that since bicarbonate and chloride are lost in this way, these substances, along with an adequate amount of water, should be given as part of the routine treatment. In practice, however, it is found to be unnecessary always to administer sodium bicarbonate as it is the Na rather than the HCO_3 which has to be replaced. Therefore, normal saline alone is given parenterally on the assumption that if the body be given both Na and Cl it will keep whichever it requires and eliminate the other in the urine provided the kidneys are functioning actively.

Of twenty-one cases of gastro-enteritis examined prior to treatment, only three had low plasma chloride values, a finding which raised the question as to the necessity of giving chloride to such cases, and as to the effect on the plasma chloride of saline administration. It seemed illogical to give additional chloride as a routine to cases of dehydration no matter whether the increase of chlorides was actual or merely relative. In pyloric stenosis, on the other hand, normal saline appeared to be the ideal fluid for parenteral administration, since the plasma chlorides are invariably lowered in this disease.

Subcutaneous therapy. As an adjunct to other treatment normal saline was given subcutaneously to fourteen dehydrated children and the changes in the blood are summarized in table 1. The blood was examined before and within the twenty-four hours following this administration. In half the children clinical improvement occurred and the red cell count, haemoglobin concentration and haematocrit readings were reduced in every patient. Chemical investigations showed that although there was a fall in the plasma chloride values in four instances, there was a rise in all other cases, in one the value being as high as 818 mgm. per 100 c.c.; also, that the concentration of plasma protein usually decreased, although this was not so marked as the reduction in red cells, haemoglobin and haematocrit.

Intravenous therapy. The results of examination of the blood chemistry before and after intravenous therapy in thirteen cases of dehydration following gastro-enteritis are shown in table 2. Clinical improvement was apparent in

TABLE 1

THE CHANGES IN THE BLOOD OCCURRING AS THE RESULT OF SUBCUTANEOUS SALINE THERAPY

CASE	AGE	CONDITION	AMOUNT OF SALINE (C.C.)	INTERVAL (HOURS)	RED CELLS		HAEMOGLOBIN PER CENT.		HAEMATOCRIT		CHLORIDE MGM. PER 100 C.C.		PROTEIN GM. PER 100 C.C.		RESULT
					BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	
3	3/12	G–E.	165	24	5·94	5·56	112	106	45·5	44·4	660	628	—	—	I.S.Q.
46	5/12	G–E.	120	24	7·06	6·84	106	96	48·3	43·8	731	818	6·97	6·04	I.S.Q.
59	5/12	G–E.	190	24	6·55	6·30	94	88	—	—	629	789	6·61	7·40	I.S.Q.
68	2/12	G–E.	100	24	4·60	4·52	86	82	39·3	34·8	678	689	4·96	4·64	Imp.
70	4/12	G–E.	160	24	5·00	4·77	82	76	40·0	36·1	537	567	6·83	6·51	Imp.
72	2/12	G–E.	275	48	5·43	4·78	93	84	44·9	40·0	582	631	7·72	6·58	Imp.
78	7/12	G–E.	240	48	6·70	5·80	102	88	45·6	38·9	672	628	7·02	6·01	Imp. P.U.
80	4/52	P.S.	100	24	5·60	5·06	108	102	48·9	45·6	526	497	6·29	6·47	Imp.
81	5/52	P.S.	100	24	5·00	4·07	100	84	43·8	38·9	569	599	6·58	6·79	I.S.Q.
88	5/52	P.S.	100	24	6·33	5·57	124	112	—	—	456	448	7·18	6·87	I.S.Q.
89	3/12	P.S.	100	24	5·29	5·11	95	88	—	—	529	559	6·10	6·72	I.S.Q.
90	6/52	G.–E.	100	24	—	—	100	98	—	—	547	606	6·22	6·04	I.S.Q.
94	4/52	P.S.	100	24	7·01	6·67	128	121	58·7	56·7	426	456	8·74	8·99	Imp.
97	3/12	P.S.	100	24	7·04	6·58	141	134	63·9	60·7	507	544	6·87	6·19	Imp.
	Average change		..	.. ..	5·96	5·51	105	97	47·9	44·0	575	604	6·78	6·56	

G.-E.—Gastro-enteritis. P.S.—Pyloric stenosis.

nine patients, three were unchanged, and one was worse after treatment. In every instance the red cell, haemoglobin and haematocrit readings fell. With two exceptions the plasma chloride values were increased despite the fact that one case received fluid which contained no chloride. In ten infants the final plasma chloride was over 700 mgm. per cent., but this did not appear to affect the patient adversely. The plasma protein was decreased in twelve of the thirteen cases.

The changes in plasma chloride after parenteral therapy

The effect of parenteral therapy on plasma chlorides deserves further attention, especially as many authorities state that administration of normal saline is essential in restoring electrolytes lost by the body, and also that such treatment does not raise the blood chlorides.

Six of the patients reported in table 1 were suffering from untreated pyloric stenosis and the others from gastro-enteritis. Only one case of pyloric stenosis had a normal initial plasma chloride value; in all other cases it was well below normal. Whereas in four instances the chloride rose to normal after the administration of subcutaneous normal saline, in two it fell still further, presumably as a result of continued vomiting. In both these infants the plasma chloride values rose to within normal limits after operation. On the other hand, before treatment four of the babies with gastro-enteritis had high chloride values, two normal values and two low values. A fall in the level of the plasma chloride followed the administration of saline subcutaneously in two of the four cases with high initial values; in one this was almost certainly due to the diuresis which occurred between the examination of the two blood samples. In the other two cases the plasma chloride readings increased to 818 and 689 mgm. per 100 c.c. respectively. In another case they rose from 629 to 789 mgm. per cent. in twenty-four hours. In those infants who received intravenous saline therapy (table 2) the plasma chloride rose to even higher values than in those which had been given normal saline subcutaneously. In nine cases in which the chloride was above normal before treatment, the final value averaged 63 mgm. per cent. higher. Although Hoag and Marples (1931) found that . . . 'vigorous treatment with parenteral fluids, including large amounts of sodium chloride, produced no significant elevation of the chloride content of the blood,' and McIntosh and his colleagues (1930–31) made similar observations, the vast majority of workers hold that the administration of large amounts of saline not only increases the plasma chloride but also causes acidosis. The discrepancy may be due to the fact that both groups of investigators delayed too long before the second examination of the blood (an average of twelve days after treatment in McIntosh's cases). My observations on the blood changes were made in almost every case from day to day over a considerable period of time, in some cases for two, three or even four weeks. In such cases the values of the plasma chloride increased as a result of treatment with parenteral normal saline, and decreased later in those cases which recovered. In view of the

TABLE 2

THE CHANGES IN THE BLOOD OCCURRING AS THE RESULT OF INTRAVENOUS FLUID THERAPY

CASE	AGE	AMOUNT OF FLUID (C.C.)	INTERVAL (HOURS)	RED CELLS		HAEMOGLOBIN PER CENT.		HAEMATOCRIT		CHLORIDE MGM. PER 100 C.C.		PROTEIN GM. PER 100 C.C.		RESULT
				BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	
21	3/12	270 (5% g–s.)	24	5·43	4·43	102	84	47·8	36·7	617	756	7·58	5·43	I.S.Q.
27	9/12	405 (10% g–s.)	24	7·21	6·68	115	107	52·3	48·9	651	687	7·40	7·07	I.S.Q.
28	6/52	240 (5% g–s.)	24	4·28	3·67	96	82	42·0	38·9	687	818	—	—	Improved
34	3/12	915 (5% g–s.)	72	5·30	4·17	92	72	43·2	32·0	687	736	7·17	5·14	Improved
42	3/12	595 (5% g–s.)	48	4·40	4·06	78	70	34·8	31·0	730	760	7·17	5·05	Improved
46	5/12	1035 (5% g–s.)	48	7·52	6·49	106	95	45·5	38·2	731	789	6·13	5·00	I.S.Q.
58	5/12	835 (5% g–s.) (10% G.) 390 (10% G.)	48	6·51	6·11	94	88	—	—	647	770	6·38	6·31	Dehydration increased
59	5/12	155 (N.S.) 240 (5% g–s.)	48	6·30	5·63	88	76	—	—	789	880	7·40	6·78	Slightly better Oliguria
65	4/12	240 (10% G.)	24	5·47	4·99	76	70	38·4	37·1	696	725	4·67	5·10	Improved
73	3/12	595 (5% g–s.)	48	5·05	4·21	90	73	—	—	750	730	5·71	4·96	Slightly better
75	5/12	200 (5% g–s.)	18	6·31	5·52	90	78	—	—	536	670	8·74	6·41	Improved.
78	7/12	130 (5% G.) 155 (5% g–s.)	24	8·02	7·05	114	100	—	—	709	731	7·22	7·15	Slightly better Passing urine
100	9/12	300 (10% G.)	18	7·20	6·69	100	84	52·2	42·8	588	502	7·86	6·91	Improved
		Average change		6·08	5·36	95	83	44·5	38·2	678	735	6·95	5·94	

G. = glucose. g–s. = glucose-saline.

statement by Boyd (1926) that the height of the plasma chloride is of no prognostic value in untreated cases, it is of interest to note the value of the plasma chloride in a few fatal cases of gastro-enteritis. All these cases were given fluid containing chloride parenterally, and almost invariably became progressively more dehydrated before they died. The findings in a few such cases are represented graphically in fig. 1, together with the values found on the day or two

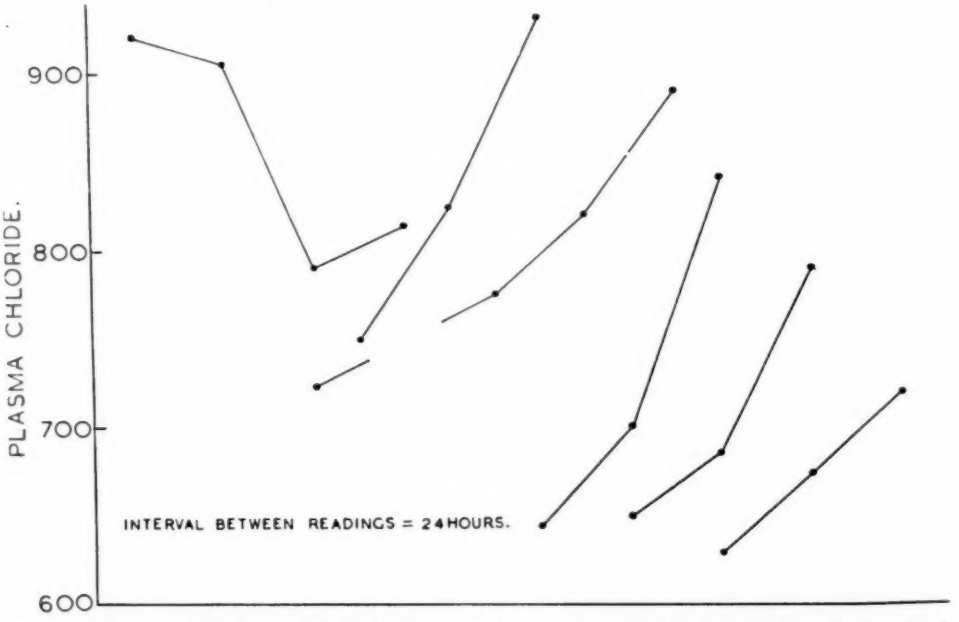


FIG. 1.—Plasma chloride values in fatal cases of gastro-enteritis in the few days immediately preceding death.

immediately preceding death. The average value of sixteen such cases was 765 mgm. per cent. NaCl.

It is important to find the explanation of the high blood chloride in the dehydration of gastro-enteritis, and its further increase as the result of treatment, since it has been demonstrated by Gamble and Ross (1924–5) that when sodium chloride is administered for dehydration, the body is able to keep the ion of which it is most in need, and, provided that renal function is active, can excrete the other in the urine.

The excretion of chloride

In the normal individual chloride is almost entirely eliminated through the kidneys and only an insignificant amount in the stools, but the fluid stools of diarrhoea may contain as much as 15 gm. of NaCl per litre. The loss of chloride in insensible perspiration is negligible and is even less than normal in dehydrated infants. The chloride output in the urine and stools of five normal and eight dehydrated infants was determined by Hoag and Marples (1931); their average results which are given in table 3 show that even in diarrhoea most of the chloride is excreted in the urine.

TABLE 3

THE AVERAGE OUTPUT OF CHLORIDE IN THE URINE AND STOOLS IN FIVE NORMAL AND EIGHT DEHYDRATED INFANTS (HOAG AND MARPLES, 1931)

	URINE OUTPUT IN 24 HOURS	URINARY CHLORIDE IN 24 HOURS	FAECAL CHLORIDE IN 24 HOURS
Normal	399 c.c.	930 mgm.	100 mgm.
Dehydration ..	327 c.c.	1218 mgm.	808 mgm.

Elimination of chloride is controlled by the needs of the body. Withdrawal of salt from an otherwise normal diet is followed by reduction of plasma chloride to about 560 mgm. per cent. NaCl at which level excretion in the urine stops so that a constant plasma value is maintained. Additional salt augments the rate of chloride excretion and raises the concentration of plasma chloride but to a surprisingly small degree in normal adults.

In spite of the fairly wide normal variation of plasma chloride (560 to 630 mgm. per 100 c.c.) it has been customary to speak of chloride as a 'threshold' substance similar to glucose. Ambard (1920) worked out a formula for the excretion of threshold substances which is said to hold good for the same individual or for persons of the same body weight. This is as follows:—

$$\frac{\text{Concentration of excess over threshold}}{\text{Rate of excretion x Concentration of urine}} = K \text{ (a constant).}$$

Aitken (1929) found that 'the nearest approximation to a renal threshold for chloride appears to be in the neighbourhood of 0·555 to 0·585 per cent. of plasma NaCl, where the above relationship is rapidly altering. There is no evidence that this neighbourhood is constant under varying physiological conditions. It is suggested that the idea of a renal threshold for chloride be abandoned.' This suggestion is supported by the few cases investigated in which there appeared to be no relationship between the excretion of chloride and the height of the plasma chloride. As a matter of fact, there is little in the literature about the normal kidney function in young infants and this has recently been the subject of investigations by McCance and Young at the Birmingham Children's Hospital, whose results are to be published shortly. Since this work of McCance and Young had not then been started, and no reference could be found to the relationship between intake of chloride and urinary output in normal infants, the intake and output of both water and chloride were estimated in a normal bottle-fed baby aged three months and the results are set out in fig. 2. This infant was taking milk and water feeds, 3 ounces three hourly, seven feeds per day, with an extra 1 to 2 ounces of boiled water during the night when necessary. Observations were made on the intake of fluid, the output of urine, the intake and output of chloride reckoned as NaCl, the haemoglobin concentration, plasma chloride and protein, and the clinical condition of the child. For three days he was given his normal feeds,

and daily estimations were made of the chloride content of the milk feeds. The individual values were 28·8, 28·1 and 28·1 mgm. per ounce of feed on the three consecutive days—an average of 0·6 gm. per twenty-four hours. On the two

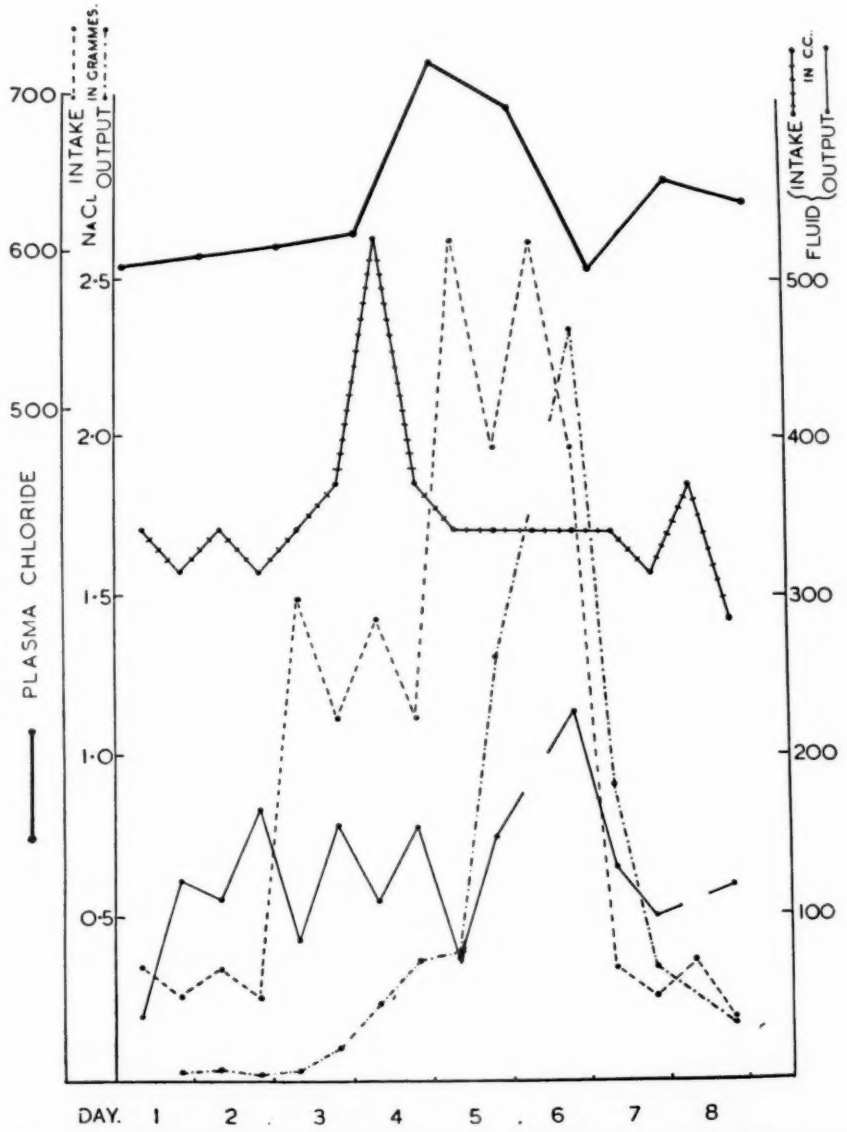


FIG. 2.—Graphic representation of the relationship between intake of chloride and urinary output in a normal child aged three months. The heavy continuous line represents the plasma chloride values. The crossed black line represents the intake of fluid in c.c. The light continuous line represents the output of urine in c.c. The dashed line represents the intake of sodium chloride in grammes. The dot and dash line represents the output of NaCl in grammes.

succeeding days, 2 gm. of NaCl were added to the twenty-four hour's feed, so that the intake of chloride was 123 mgm. per ounce of feed. The baby took the feeds quite well, and apart from being rather irritable and thirsty for twenty-four hours, appeared to be none the worse. During the subsequent two days

4 gm. of NaCl were added to the feeds for twenty-four hours, and for the remaining days on which he was examined no additional NaCl was given. In the graph the plasma chlorides and other constituents of the blood are shown as the value at 10·0 a.m. on each day. The other estimations, being entirely quantitative, are divided into two twelve-hour estimations; the advantage of so doing is especially noticeable in the case of the urine volume. The actual collection of urine was always the most difficult procedure, and occasionally specimens were upset or voided into the bed, but working on a twelve hour basis meant that the loss of a specimen only affected the estimations over half a day. Unfortunately, the only important specimen lost in the case under consideration was that of the first period of the sixth day, quite the most important specimen of all. At this point the intake of chloride was at a maximum, the intake of fluid had fallen to normal, the output of chloride was increasing to its maximum, and the plasma chlorides were returning to their previous level; indeed, the concentration of chloride in the urine was 1·39, only just below the usually accepted maximum concentration at which the kidney excretes chloride (1·5 to 2·0 per cent.).

There are several features of interest about this case. First, the oral intake of fluid is about two-and-a-half times as large as the output of urine over the same period. As the chloride in the diet was increased, the infant became distressed and extremely thirsty. It would have been interesting to withhold water at this stage, but, anticipating the thirst, orders had been given that the child was to have as much extra water as he wanted. In spite of the greatly increased fluid intake on the fourth day, it was not until forty-eight hours later that diuresis occurred, although the concentration of chloride in the urine had been steadily increasing since the administration of the extra amount. The water taken had presumably been stored in the tissues with the excess of NaCl in order to keep the extra-cellular body fluids isotonic. The child almost certainly gained two or three pounds in weight at this stage, and lost them again when he had the diuresis, but unfortunately daily weighings were not carried out lest specimens of urine should be lost. Similar effects from excess NaCl by mouth have been described by de Wesselow (1924) and also by Junkenitz (Peters, 1935) who remarked that since he had found only a slight increase in the plasma chloride (24 mgm. per cent.) the blood must have been diluted by fluid from the tissues. In the present case the plasma chloride rose from 600 to 700 mgm. per cent. NaCl, but rapidly became normal after the excess of chloride had been removed in the urine.

Another and most important point in the consideration of the question of administering chloride to cases of diarrhoea and vomiting with dehydration is illustrated in the graph (fig. 2). On the fifth, sixth and seventh days, the concentration of chloride in the urine was greater than that in the feeds, and at one point almost reached the maximum value possible (1·5 per cent.) although the concentration in the feeds only reached 0·75 per cent. on two successive days. Since the urinary output is considerably less than the fluid intake, if nothing but normal saline were administered it would be quite impossible for the body to get rid of the excess chloride because if not more than one half of the amount of water

taken in by mouth is excreted through the kidney, then the concentration of chloride in the urine would have to be at least twice as great as its concentration in the oral fluid; thus, if the only fluid given is normal saline (0·9 per cent.) the concentration of chloride in the urine must be at least 1·8 per cent., a figure that is above the usually accepted maximum of 1·5 per cent. If there is oliguria, chloride retention is certain, and if there is also a water deficit the concentration of chloride in the blood must rise, yet despite these facts, infants who are unable to take fluid by mouth because of vomiting are frequently given large quantities of normal saline parenterally. For instance, a patient who was put on a continuous intravenous drip infusion of 5 per cent. glucose in normal saline, received 1190 c.c. in just over three days. The output of urine increased, but although the concentration of chloride in the urine increased from 0·03 to 1·4 per cent., the plasma chloride continued to rise (fig. 3) until the child died.

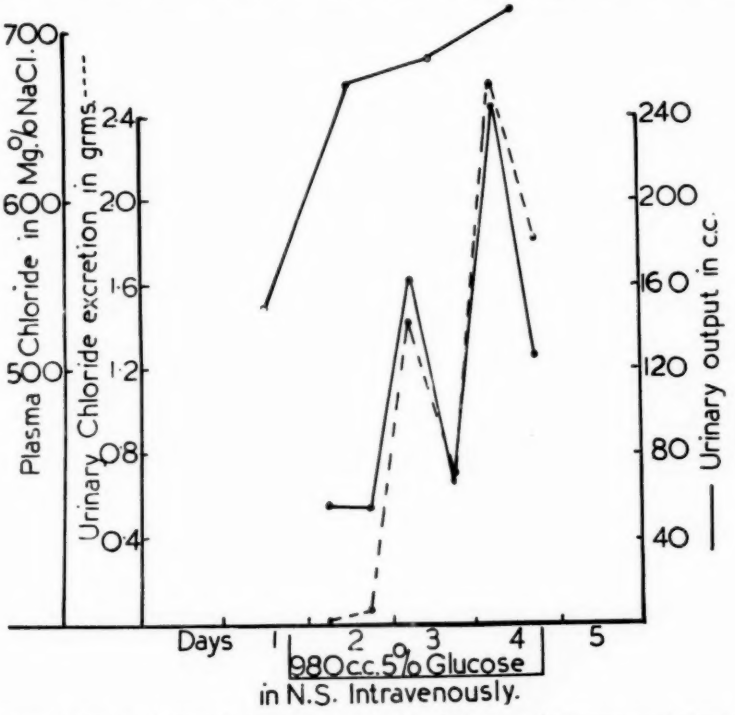


FIG. 3.—Chart showing increasing plasma chloride following intravenous injection of 5 per cent. glucose in normal saline, despite the increase in urinary flow and increased concentration of chloride in the urine.

As a result of these investigations it was decided that the routine administration of fluids containing normal saline was both illogical and unsafe; nevertheless, there are cases of gastro-enteritis which need chloride, and the only way to determine when this treatment should be used is by carrying out frequent examinations of the blood.

For the relief of oliguria the fluid of choice must not only be such as to supply water to the organism to counteract dehydration, but must also assist in restoring the disordered blood chemistry to normal, chiefly by virtue of its diuretic action. For this purpose, hypertonic glucose (10 per cent.) is most commonly

used and was given to a few patients. Its action is well shown in fig. 4: after twenty-four hours oliguria (9·6 c.c. of urine only), 260 c.c. of 10 per cent. glucose were given intravenously; there was an immediate diuresis which was maintained by subsequent administration of 380 c.c. of 5 per cent. glucose in normal saline intravenously, together with saline given subcutaneously. A large amount of chloride was excreted in the urine, and the plasma chloride which had risen above normal fell to within normal limits.

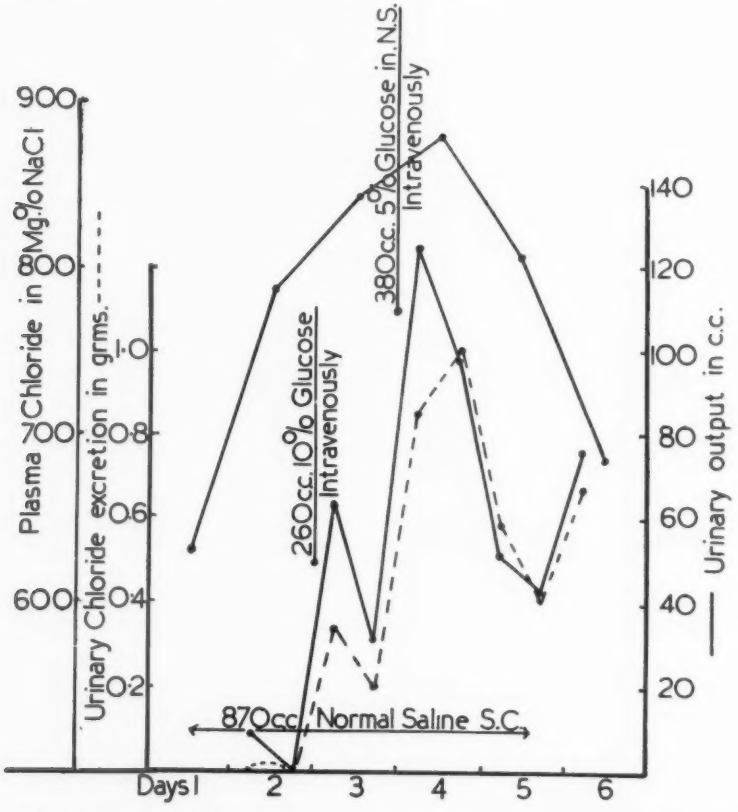


FIG. 4.—Showing the effect of intravenous administration of hypertonic glucose, 5 per cent. glucose in normal saline, and saline subcutaneously, on the quantity of urine secreted and on urinary and plasma chloride.

There are, however, two objections to the haphazard intravenous infusion of 10 per cent. glucose. First, it is possible to remove chloride from the organism, even when there is not an accumulation of chloride in the blood, and hence the plasma chloride may fall considerably below normal. If this were allowed to continue so much chloride might be lost that tetany might ensue, as in the case of pyloric stenosis. In one patient this treatment reduced the plasma chloride from 588 to 502 mgm. per 100 c.c. NaCl, although tetany has not been observed. Secondly, by producing a marked diuresis in a patient who can only take a little fluid by mouth and is also losing much fluid as the result of diarrhoea, the use of 10 per cent. glucose solution may increase the degree of dehydration. Such a result was seen in a child after the administration of 160 c.c. of the glucose intravenously. This child was able to take only 11½

ounces of fluid orally during twenty-four hours, but in the twenty-four hours after infusion he passed 4 ounces of urine; although his clinical condition remained unchanged, examination of the blood showed that red cells and haemoglobin concentration had risen from 7,170,000 and 100 per cent. to 8,020,000 per c.mm. and 114 per cent. respectively. Subsequently he improved rapidly after he had been given 5 per cent. glucose in water in half-normal saline intravenously, together with normal saline subcutaneously. Many authorities advocate the combined use of these solutions; certainly this method does away with many of the pitfalls of parenteral fluid therapy, and has proved the most suitable fluid for routine intravenous therapy in dehydration.

Finally, there are two other objections to the use of a large volume of fluid intravenously in treatment of dehydration. First, the plasma protein may fall considerably, and secondly, oedema of the intestinal mucosa may occur and lead to intensification of the diarrhoea (Karelitz, 1931).

BLOOD TRANSFUSION IN THE TREATMENT OF DEHYDRATION

Historical. During the past ten or fifteen years many authorities have recommended transfusion of whole blood in the treatment of the dehydration which arises from gastro-enteritis in infancy, some recommending transfusions as a routine procedure and others reserving their use for cases which failed to respond to other therapy.

Marriott (1934) advised blood transfusion in cases of chronic anhydraemia in order to restore to normal the blood volume which had been reduced by the destruction of red cells and plasma protein. Powers (1926) described blood transfusion as the most potent method of treatment for ' alimentary intoxication ' recommending its use almost as a routine about an hour after the parenteral administration of other fluids and, if necessary, repeating it at intervals of twenty-four hours. In the same year, Carlton suggested that a blood transfusion should be given to all infants with ' acute intestinal intoxication.' In his series of 139 cases, 70 per cent. were improved and the ultimate mortality rate was reduced to 37 per cent. Similar approval was expressed by Sidbury (1927) who described a series of 111 cases with a mortality figure of only 28 per cent.; he also suggested the preliminary administration of fluid, presumably intravenously, if the infants were very dehydrated. Johnson (1931) reduced his mortality rate in gastro-enteritis from 78 per cent. to 64 per cent. by means of transfusion, and Karelitz (1931) claimed improvement in all of thirty cases of ' alimentary intoxication ' treated with 5 per cent. glucose in normal saline followed by blood transfusion. Thomson (1935) advocated the use of transfusion in marasmic children who were not progressing, but he found that it often gave disappointing results in the extreme stages of gastro-enteritis.

Butler (1935) and also Marriott and Hartmann (1933) advised the use of blood transfusion to raise the plasma protein when for any reason this was low, but the latter workers pointed out that in dehydrated infants whose plasma protein was already high as the result of fluid lost from the blood, transfusion might raise the protein to an even higher level, and so cause embarrassment to the circulation. The use of blood transfusion was advised by Holt and McIntosh (1933), ' since the fluid is retained for a longer time,' and Spence (1933) stated that it might be of great therapeutic value in advanced cases of gastro-enteritis, whilst Brown and Tisdall (1937) recommended its use if there

was any marked drowsiness. Wiener (1935) expressed the opinion that although of little value when used alone, blood transfusion played a part in retaining the body fluids when used in conjunction with the administration of normal saline and glucose solutions. Maizels and Smith (1934), on the other hand, reported twenty cases of severe gastro-enteritis treated with blood transfusion of which only three improved clinically, and Cooper (1937) found the results disappointing in eighteen cases of acute gastro-enteritis. He suggested that blood transfusion was most useful in cases of chronic diarrhoea in which the blood was actually lacking in red cells and plasma protein, but he also pointed out that there was a danger of causing an increase in the protein by the administration of blood to infants suffering from acute diarrhoea.

The results and mortality figures reported by writers therefore vary greatly and Johnson (1931), when discussing 'alimentary intoxication,' makes the pertinent observation that 'when some authors say that the disease is almost always fatal, and others report 75 per cent. recoveries, it is evidence that they do not include the same type of case in their studies.' Theoretically, at least, blood appears to be the ideal fluid to give dehydrated infants with gastro-enteritis. The diminished volume of circulating blood is thereby increased; moreover colloid suspensions, such as blood, are said to attract fluids into the circulation and to retain them more efficaciously than do crystalloid solutions, such as glucose and saline. Blood supplies food to the organism and the antibodies which it contains assist in combating any infection from which the recipient may be suffering; furthermore, whole blood is a physiological fluid. On the other hand, the question arises as to whether the administration of whole blood to a child whose blood is already concentrated will not increase the degree of haemo-concentration and so cause deterioration of the clinical condition. It is obvious that the red cell count, haemoglobin concentration and haematocrit reading rise after transfusion in anaemic patients, and the extent to which this occurred in twelve children of all ages is shown in table 4. It is of interest to note that the average change in the plasma protein was a slight fall, although in those cases in which the donor's blood was examined the plasma protein was not found to be unduly low.

Investigation

During recent years at the Birmingham Children's Hospital, blood transfusions have been given to dehydrated infants suffering from gastro-enteritis, and although a small number improved rapidly after this treatment the majority did not, and actually became worse. In a few instances, death occurred within a few hours of transfusion, and in the course of a single year three infants died during or immediately after this treatment. In the light of such results the wisdom of giving transfusions of whole blood to dehydrated infants was considered, and also the reason why some children showed deterioration in the general condition, whereas others improved. To this end, investigations were carried out similar to those used in the enquiry into the effects of parenteral fluid therapy; thus changes in the red cell count, haemoglobin concentration, haematocrit reading and plasma protein content were studied. These observa-

TABLE 4

THE CHANGES IN THE BLOOD WHICH RESULT FROM THE TRANSFUSION OF WHOLE BLOOD IN DEHYDRATION

CASE	AGE	CONDITION	AMOUNT OF BLOOD (C.C.)	INTERVAL (HOURS)	RED CELLS		HAEMOGLOBIN PER CENT.		HAEMATOCRIT		PROTEIN GM. PER 100 C.C.		RESULT
					BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	
3	3/12	D. and V.	80	4	5·06	5·41	90	98	37·7	41·1	—	—	Improved
10	3/12	D. and V.	60	21	5·71	6·09	96	106	42·2	44·4	—	—	Condition worse during B.T.
26	9·52	Dehydn.	30	16	5·57	5·82	106	114	48·9	50·6	7·10	7·87	Slight improvement
35	6/12	D. and V.	40	20	7·45	8·12	98	108	54·0	56·2	6·98	6·32	Worse
39	6/52	D. and V.		18	5·55	6·22	104	122	43·3	49·4	6·51	6·54	Worse
44	5/12	D. and V.	55	18	6·53	7·77	96	110	50·0	53·2	7·72	7·53	Worse
47	8/12	Coeliac	70	20	6·29	6·52	98	100	47·3	48·1	6·72	6·32	I.S.Q.
52	9/52	D. and V.	30	20	6·03	5·90	106	100	52·2	51·5	6·38	5·93	I.S.Q.
75	5/12	D. and V.	120	16	5·71	6·59	84	120	—	—	5·29	5·87	Worse
85	11/52	D. and V.	60	21	4·85	5·66	84	94	—	—	7·02	6·91	Slight improvement
91	6/12	D. and V.	60	4	6·35	6·80	66	68	—	—	5·71	6·83	Slight improvement
91	6/12	D. and V.	80	16	5·90	7·25	59	76	32·6	41·0·	5·17	5·10	Slight improvement
		Average change ..		.. ..	5·92	6·51	91	101	45·4	48·4	6·46	6·52	

tions were made on twelve infants, and the results of the investigations are set out in table 4. In all but one instance the readings of red cells, haemoglobin and haematocrit increased considerably, irrespective of the size of the transfusion and of the time between the taking of the two blood samples. On the average the plasma protein content was slightly decreased. Five babies were a little improved, two unchanged, and five were definitely worse after transfusion.

Because of the increased concentration of the blood produced by the transfusion of citrated blood, it was thought that if fluid such as normal saline or solutions of 5 or 10 per cent. glucose in normal saline were given simultaneously with the blood, the increase of haemo-concentration would be avoided. Twelve infants were treated in this way and the results are shown in table 5. Six of the cases showed some degree of improvement clinically, but others became much worse. In two instances there was no appreciable change in the concentration of the blood and in only one was there a decreased concentration. Estimations of the plasma protein were made in six cases and the average value rose slightly after transfusion.

In fig. 5 the immediate effect of blood transfusion in a case of gastro-enteritis is illustrated. The interesting feature of the case is the inverse variation of the

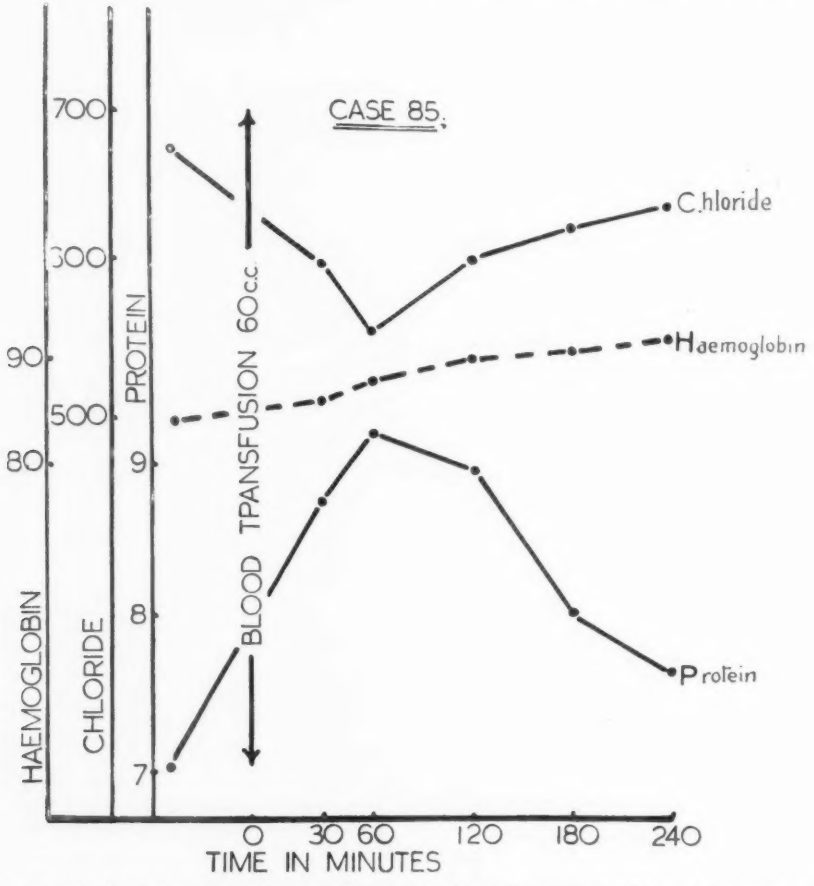


FIG. 5.—Graph showing the effect on blood chloride (C), protein (P), and haemoglobin (H) during a period of four hours following a blood transfusion for dehydration.

TABLE 5

THE CHANGES IN THE BLOOD WHICH RESULT FROM THE TRANSFUSION OF BLOOD PLUS SALINE IN DEHYDRATION

CASE	AGE	CONDITION	AMOUNT OF BLOOD (C.C.)	AMOUNT OF SALINE (C.C.)	INTERVAL (HOURS)	RED CELLS		HAEMOGLOBIN		HAEMATOCRIT		PROTEIN GM. PER 100 C.C.		RESULT
						BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	
2	8/12	D. and V.	80	20	22	6·00	5·66	92	84	46·7	39·3	—	—	Cyanosed during B.T. Haematemesis and haematuria
4	5/12	D. and V.	50	50	18	6·01	6·12	114	132	44·4	51·1	—	—	Worse: cyanosed during B.T.
12	3/12	D. and V.	50	40	4	5·96	6·37	102	122	48·3	60·0	—	—	Slightly better
16	5/12	D. and V.	140	20	17	4·82	6·45	72	94	34·8	48·4	5·60	6·68·	Worse: fingers cyanosed next day
20	3/12	D. and V.	120	20	18	4·28	5·40	76	98	38·2	48·4	—	—	More dehydrated after B.T.
28	7/52	D. and V.	60	DRIP	18	4·59	4·67	94	95	38·2	38·9	—	—	Slightly better
32	5/52	D. and V.	80	DRIP	18	5·42	5·43	112	112	48·3	50·5	—	—	Slightly better
33	6/12	D. and V.	90	DRIP	18	5·75	6·56	104	106	47·3	50·6	7·76	7·48	Worse
45	4/52	D. and V.	40	DRIP	17	4·92	5·27	98	104	42·7	48·3	5·27	5·23	Improved : turgor increased
64	3/12	D. and V.	100	DRIP	18	4·77	5·63·	82	92	39·4	43·8	5·56	4·75	Improved
65	4/12	D. and V.	60	60	13	5·66	6·37	82	90	39·3	42·5	4·91	5·95	Much worse
105	5/12	D. and V.	45	40	16	5·96	5·55	77	80	35·0	36·7	7·77	7·62	Improved
		Average change				5·35	5·79	92	101	41·9	46·5	6·15	6·29	

protein and chloride due presumably to an attempt to keep the osmotic pressure of the blood constant.

Contra-indications to blood transfusion. Deterioration following blood transfusion in a patient is shown graphically in fig. 6. The blood picture and clinical condition of this child were growing worse when 60 c.c. of blood were given. On the following day the child was even worse, and was becoming more dehydrated as a result of diarrhoea. A day later still it was impossible to procure a blood sample owing to the extent of the cyanosis and congestion of the feet, and the child died on that day. The graph shows the rise of plasma chloride to 838 mgm. per cent. and the increase in blood concentration as the condition of the child deteriorated.

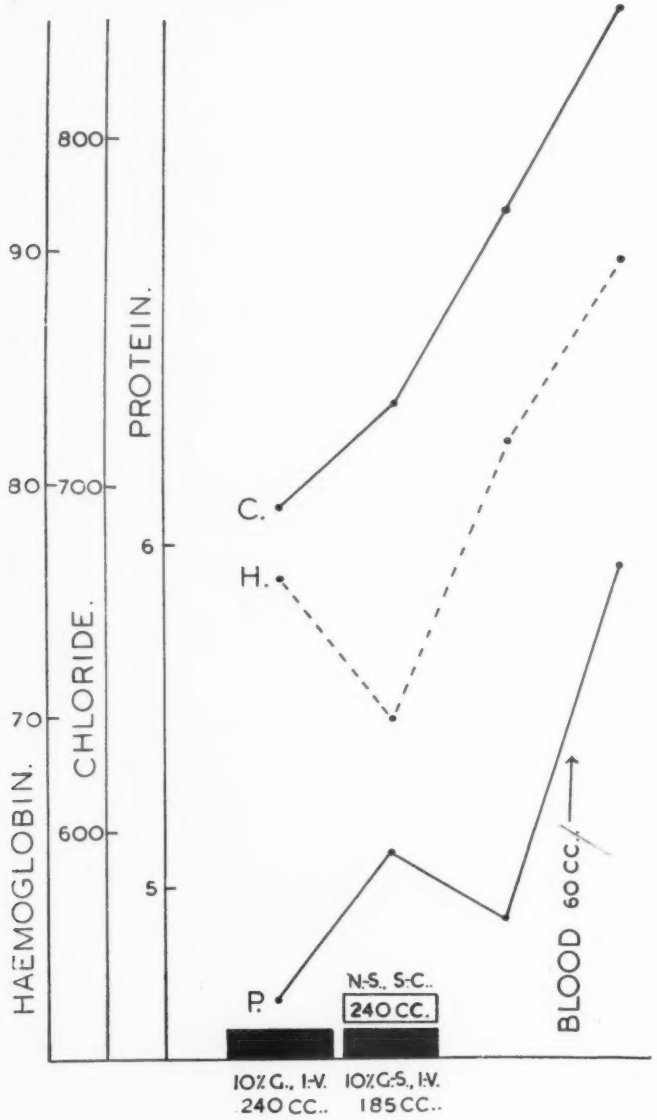


FIG. 6.—Graph showing the deleterious effects on blood chloride (C), haemoglobin (H) and blood protein (P), produced in an infant as a result of blood transfusion.

If it is possible to exclude such factors as too large a transfusion, too rapid administration, an error in grouping, cross agglutination between donor and recipient, the presumption that the unsatisfactory results are due to the transfusion itself appears a justifiable one. These factors will now be considered:—

DOSAGE. Most authorities advise the giving of a maximum of from 10 to 15 c.c. per pound of body weight. (Johnson, 1931; Maizels and Smith, 1934; Goldsmith, 1932; and Spence, 1933.) Holt and McIntosh (1933) state that in dehydration 'it is unwise to inject at one time more than 10 c.c. per pound of body weight.' It is therefore surprising that a few observers have advocated the use of larger amounts; Karelitz (1931) gave up to 40 c.c. per kilogramme but noted severe reactions in many cases. Thomson (1935) found that in babies with marked dehydration amounts larger than 15 c.c per pound could be given with safety, and Powers (1926) considered that babies in general, and those with intestinal intoxication in particular, stood transfusions extraordinarily well. He gauged the dosage of blood by the degree of dehydration, the greater the dehydration the larger the amount of blood given. At the Birmingham Children's Hospital the commonly accepted maximum figure of 15 c.c. per pound is never exceeded. In particularly ill children, the tendency is to give smaller amounts, and in these dehydrated infants the amount given was between 5 and 10 c.c. per pound of actual weight. Neither the previous maximum weight nor the expected weight was taken into account; with this procedure the ill effects noted after transfusion could not be due to the administration of an excessive amount of blood.

RATE OF ADMINISTRATION. The blood was always given as slowly as reasonably possible, from three to four minutes being taken for every 20 c.c., hence any subsequent ill effects were unlikely to be the result of an excessive rate of transfusion. Apart from the obvious danger of overloading the circulation by the too rapid injection of blood, infants become very restless when the blood is given too quickly; whereas, if the blood is given at the rate described, they will take a feed quietly or may even go to sleep during a transfusion. Part of the restlessness is due, no doubt, to pain which results from distension of the vein by which the blood is being given.

BLOOD GROUPING. Apart from grouping both donor and recipient, it was the rule to carry out cross-agglutination tests both between the donor's cells and the recipient's serum, and also between the recipient's cells and the donor's serum. In one instance when the infant subsequently had haematemesis and haematuria, the cross agglutination tests were repeated after transfusion, bu no agglutination was found to occur.

It seems, therefore, that the amount of blood given, the rate of its administration and the grouping can all be excluded as the factors responsible for the unsatisfactory results obtained.

Discussion

It is interesting to note that some of the cases which improved after transfusion had microcytic anaemia as shown by the low colour index (the lowest

being 0·5), and an apparently normal initial haematocrit reading of under 40. These infants, before they became dehydrated, must have had a blood count of from 4·0 to 6·0 million red cells, a haemoglobin of about 50 per cent. and a haematocrit reading of from 25 to 30, but as a result of dehydration and anhydraemia all these values became increased until the haemoglobin and haematocrit readings, at least, were within normal limits. This condition has been referred to as ' masked anaemia.' It is easy to understand why such cases may improve after transfusion, for even after this procedure the ratio of the packed red cells to the plasma fraction of the blood (as determined by the haematocrit) is little, if at all, increased above the normal value. Consequently, the circulation is not embarrassed by an increase in concentration and viscosity of the blood. Unfortunately, it was impossible to obtain haematocrit figures in every patient, but it is instructive to compare initial and subsequent haematocrit readings in eight patients who improved with a similar number who failed to show improvement after transfusion (see tables 4 and 5). The average initial value in those infants who improved was 40·4 and this was increased 3·5 by transfusion to an average figure of 43·9. Two children had subsequent values of over 50, but the actual increase was only 1·7 and 2·2 respectively. The average amount of blood given was 61 c.c. and the average age of the patients was three months. In the children who became worse after transfusion, the average initial value was 44·4 and the value after transfusion 49·5, an increase of 5·1. In four cases the second reading was over 50, the average increase in these being 3·9. The amount of blood per transfusion averaged 71 c.c. (for seven cases), the average age being four and a half months. Therefore, not only was the initial value higher in the patients who failed to improve clinically, but in addition the average increase was greater than in those cases which improved. From the figures it can be seen that of the dehydrated children who were transfused those with the greatest haemo-concentration (i.e., the highest haematocrit readings) gave the least favourable clinical results, and they also showed a greater increase in the concentration of their blood after they had received the transfusion.

It is hence of the greatest importance to assess the degree of haemo-concentration present in a dehydrated infant, before deciding whether or not to give a blood transfusion. Moreover, routine blood transfusions in the treatment of dehydration in infancy seem quite illogical, not only in view of the facts revealed in these investigations, but also because in the first two or three days after transfusion the blood volume remains increased solely by the volume of injected red corpuscles (Boycott and Oakley, 1934), and because infusion of whole defibrinated blood to dogs causes plasma rapidly to leave the blood stream (Adolph et al., 1934). There is little weight in the argument that the extra protein introduced by transfusion attracts fluid into the blood stream, because in spite of an increase in the concentration of the blood, the plasma protein may actually fall after transfusion; moreover, if the child's own protein cannot hold fluid in the circulation, it is difficult to believe that a similar concentration of protein from a donor's blood can attract fluid from the tissues into the blood stream.

PLASMA TRANSFUSION IN THE TREATMENT OF DEHYDRATION

In the light of the disappointing results and of the increased haemo-concentration following blood transfusion, it was decided to try the effect of transfusion of plasma in cases of extreme dehydration. It was hoped by the use of plasma to give the patient the beneficial stimulus of a blood transfusion without increasing the concentration of his blood by the addition of red cells since it is the plasma fraction of the blood which is reduced in dehydration (Spence, 1933). Karelitz in 1931 mentioned the use of plasma in dehydrated infants whose haemoglobin was over 65 per cent., but he found the preparation of plasma took so long that he abandoned its use. Hartmann (1934) also referred to the use of plasma transfusion in the treatment of starvation oedema.

The plasma used was prepared by centrifuging citrated blood for half an hour at 3,000 revolutions a minute, and it was usual to obtain about 30 c.c. of plasma from each 50 c.c. of citrated blood. Eight patients were treated in this way, and it must be stressed that all were desperately ill. Table 6 shows the degree of concentration of the blood before and after treatment. Four cases had appreciable amounts of 5 per cent. glucose in normal saline given at the same time as, or just after the plasma; the remaining cases had no other fluid parenterally. Of these eight children four eventually died, but so far as the immediate results were concerned, five were clinically improved, two became worse, and the others did not show any change. In six of the cases, haemo-concentration was diminished and as with whole blood transfusions the concentration of plasma protein was, on the average, decreased.

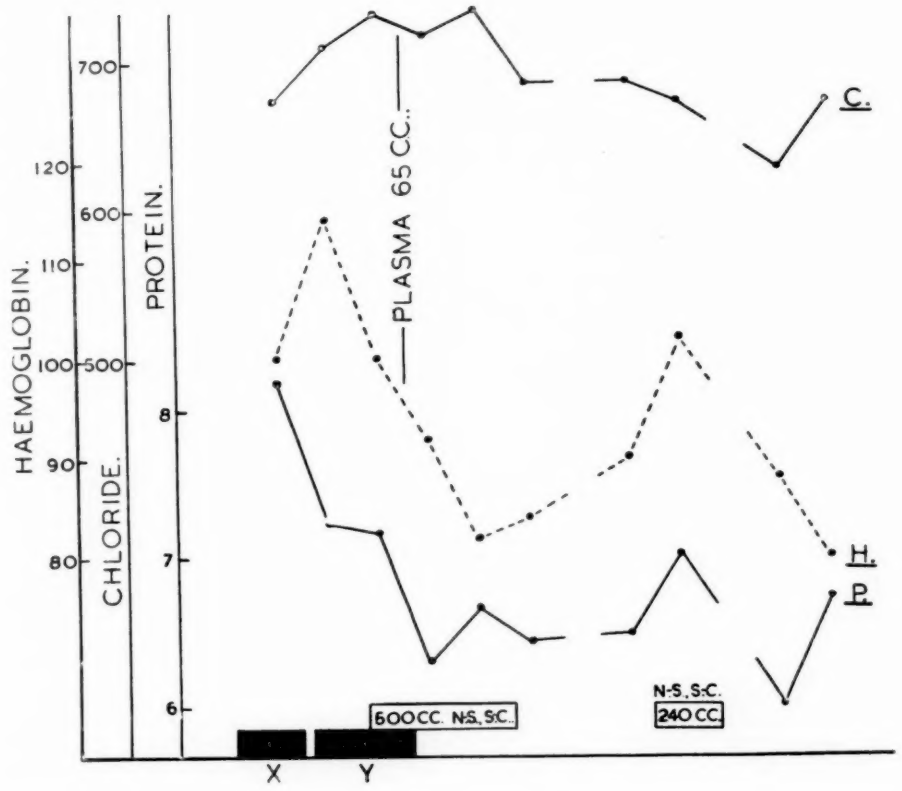
The effects of plasma transfusion in an individual case are shown in fig. 7 and 8. This child was suffering from gastro-enteritis, and was very toxic and dehydrated. There was marked concentration of the blood (red cells 7·17 millions, haemoglobin 100 per cent., haematocrit not estimated), but the administration of 160 c.c. of an aqueous solution of 10 per cent. glucose (X in fig. 7) caused no improvement, in fact the red cells rose to 8·02 millions, and haemoglobin to 114 per cent. Subsequent administration of 435 c.c. of glucose and saline (Y in fig. 7) produced improvement. On the third day, 65 c.c. of plasma were given intravenously. Apart from a pyrexia of 106° F. no untoward reaction occurred, and there was a further slight improvement in the clinical condition, despite continued diarrhoea and vomiting. However, the blood became and remained much less concentrated (red cells about 6·00 millions and haemoglobin 85 per cent.) suggesting that the plasma assisted in retaining a large amount of the injected fluid in the blood stream. The effect of treatment on the urinary output and chloride is shown in fig. 8; the intravenous injection of fluid started a relative diuresis, and when chloride began to be excreted in the urine the plasma chloride fell from 735 mgm. to 628 mgm. per cent., in spite of twenty-four hour's anuria on the ninth day. The clinical condition improved greatly, the child was taking well by mouth, and his tissue turgor was restored almost to normal.

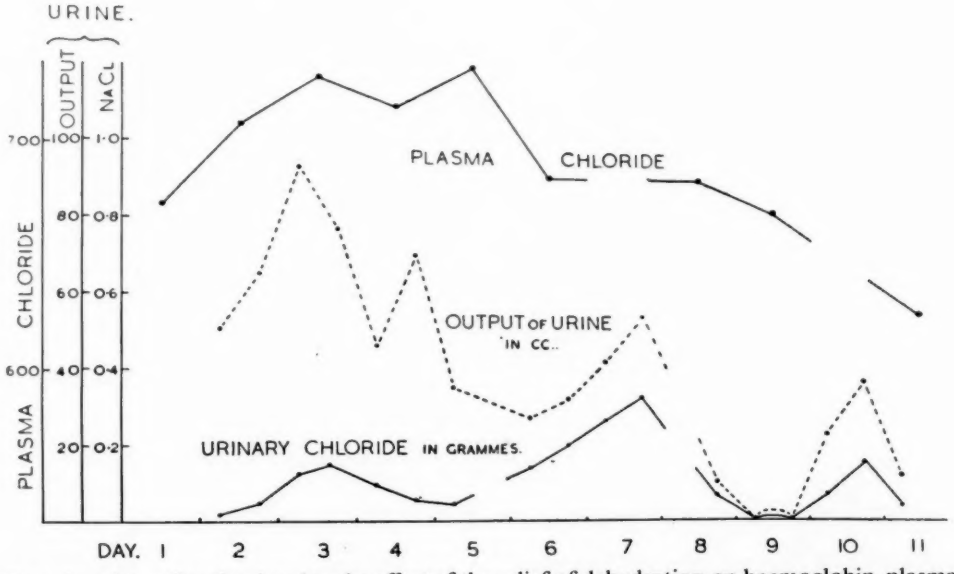
The immediate effects of plasma transfusion are demonstrated in fig. 9. This infant was very dehydrated and toxic as a result of gastro-enteritis; her

TABLE 6

THE CHANGES IN THE BLOOD WHICH RESULT FROM THE TRANSFUSION OF PLASMA IN DEHYDRATION

CASE	AGE	CONDITION	AMOUNT OF PLASMA (C.C.)	INTERVAL (HOURS)	RED CELLS		HAEMOGLOBIN PER CENT.		HAEMATOCRIT		PROTEIN GM. PER 100 C.C.		RESULT
					BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	
56	6/12	Toxic: very dehydrated	70	24	6·50	5·95	84	75	—	—	6·98	5·65	Much improved
67	9/12	Toxic: very dehydrated	75	16	7·80	7·82	98	98	47·0	47·2	5·66	5·32	Worse. T. 105° F.
71	4·12·	Not very toxic	175 (drip)	18	5·64	5·50	84	82	38·9	37·1	5·63	5·39	No improvement
73	3/12	V. severe diarrhoea	150 (drip)	18	5·65	5·05	104	90	45·6	36·9	5·71	5·71	Slightly better : T.P.R. raised
78	7/12	Very toxic: pneumonia	65	16	7·05	6·26	100	92	—	—	7·15	6·31	Slightly better: temp raised
111	5/12	Toxic: very dehydrated	50	21	6·62	5·88	105	98	49·5	44·4	8·01	8·22	Immediate condition improved
113	12/12	Toxic: very dehydrated	120	16	6·58	6·46	85	82	44·4	39·4	6·55	6·80	Immediate condition improved
114	10/12	Toxic and dehydrated	125	16	6·66	6·51·	86·	85	42·5	42·8	7·35	6·16	Worse: dehydration increased
		Average change			6·56	6·18	93	88	44·7	41·1	6·63	6·20·	





FIGS. 7 and 8.—Graphs showing the effect of the relief of dehydration on haemoglobin, plasma protein and chloride and also on the urinary output and chlorides.

red cells numbered 7·03 millions per c.c., haemoglobin 108 per cent. and haematocrit 48·9. 200 c.c. of normal saline were given subcutaneously, but she remained critically ill and 50 c.c. of plasma with 20 c.c. of normal saline were given intravenously. The concentration of the blood was decreased, the haemoglobin falling to 94 per cent. and the haematocrit to 43·3. There was an

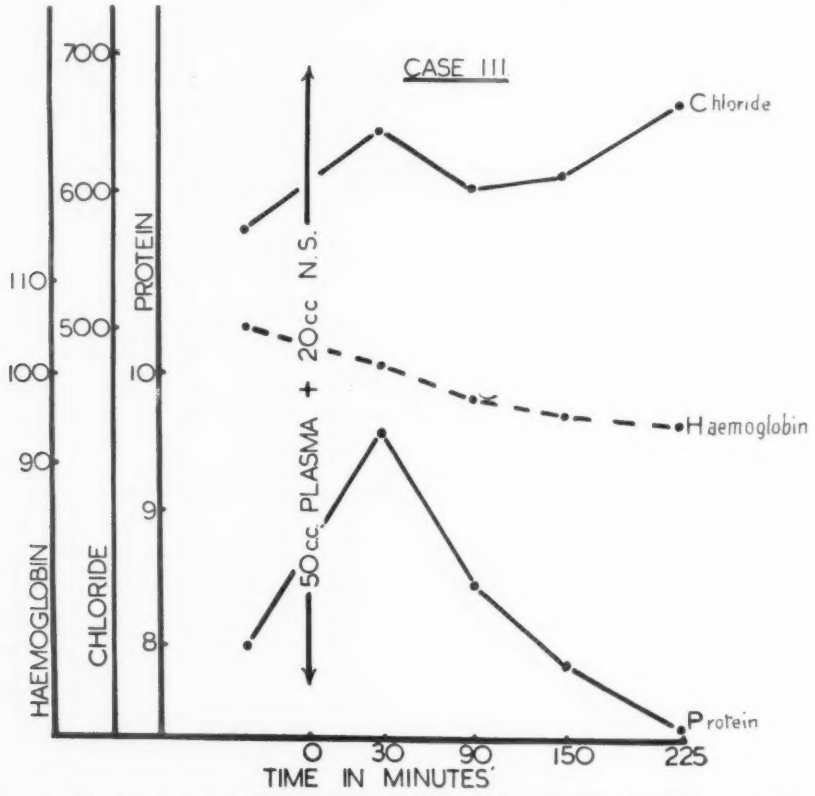


FIG. 9.—Graph showing the effect on haemoglobin (H), blood protein (P), and chloride (C) in dehydration during a period of four hours after administration of blood plasma.

immediate rise in protein concentration and then a fall to a figure which was a little lower than the initial value. In the meantime, there was a considerable improvement in the clinical condition, but later there was a return of the vomiting, she became rapidly worse and eventually died.

CONCLUSIONS

Solutions of normal (0·9 per cent.) saline should not be used as routine treatment in dehydration from gastro-enteritis; in many instances there is an apparent, if not actual, accumulation of chloride in the blood which may increase if further chloride is administered. The routine use of whole blood in the treatment of dehydration is not recommended, as in the majority of cases the blood, which is already concentrated, becomes even more so as the result of treatment. When considering the use of blood transfusion the haematocrit, and preferably the red cell count and haemoglobin concentration in addition,

should be estimated. If these are raised above normal the case is unsuitable for transfusion. In those patients in whom the haematocrit shows a marked degree of haemo-concentration and who require more drastic treatment than the administration of crystalloid solutions parenterally, transfusions of plasma should be undertaken.

The methods used in these investigations were described in a previous paper (Aldridge, 1941).

In the preparation of this and the preceding paper, thanks are due to Miss Eva Tonks for carrying out a large number of biochemical investigations; to the Nursing Staff of the Hospital without whose loyal co-operation these investigations could not have been carried out; to Prof. Leonard G. Parsons and Dr. J. M. Smellie for criticism and advice, and finally to the Medical Research Council for defraying the expenses of the work.

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CASE REPORT

A CASE SHOWING COMBINED FEATURES OF ACUTE RHEUMATISM AND RHEUMATOID ARTHRITIS

BY

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(From the Children's Unit, Hempstead House Emergency Hospital)

'There are not two fundamentally distinct diseases to be dealt with, as certain authors fancy, but only two different manifestations of one and the same diathetic state,' wrote Charcot in 1881, but at the present day there still remain two opinions, one supporting the above-mentioned theory, the other supporting the view that acute rheumatism and rheumatoid arthritis are two distinct and independent entities.

Acute rheumatism characteristically attacks children or young adults, starting suddenly with fleeting pains in the joints which become swollen and acutely tender, soon subsiding and leaving no permanent defect. The heart shows signs of carditis, the temperature is raised, and nodules may appear on the tendon sheaths and bony prominences. In contrast, rheumatoid arthritis usually attacks older people, is more insidious in onset, involving the smaller joints of hands and feet as well as the larger ones, resulting in a diffuse periarticular thickening and limitation of movement. The joints of the fingers acquire a characteristic spindle shape and the hands show an ulnar deviation. Ultimately the condition in the chronic stage gives rise to crippling deformities. There are no clinical signs of carditis, and nodules when they occur are more insidious in onset and more persistent (Bennett et al., 1940). Between these two very different clinical pictures numerous varieties have been described correlating the two conditions. Still (1897) described the condition in children with an associated enlargement of spleen and lymph glands and Felty's syndrome is a similar condition in adults (Weber, 1937).

There is some doubt as to the frequency of cardiac involvement in rheumatoid arthritis.

Master and Jaffe (1934) claim to differentiate acute rheumatoid (infective) arthritis in adults from acute rheumatic fever by the absence of clinical signs of organic heart disease and absence of changes depicting myocardial involvement in the electrocardiograph. Still (1897), in his original description, found physical signs of adherent pericardium in two out of twelve cases and in the only three autopsies performed found the pericardium to be universally adherent in all, these patients having given no physical signs of the condition during

life. In the three autopsies only one showed thickening of the mitral valve. Colver (1937), in a follow up of forty-nine cases, could find no clinical evidence of valvular lesion but states ' adherent pericardium on the other hand is a recognized complication and was found in two of the autopsies and one of the surviving patients.' Four autopsies were performed.

In the pathology of the two conditions Collins (1939) points out that the gross appearances are different, the histological similarities occurring in tissues not highly differentiated and therefore liable to react similarly to a variety of agents. Bennett, Zeller and Bauer (1940) go further than this in their study of the nodules, stating ' they differ as much from one another as do syphilis and tuberculous granuloma, suggesting they may be due to different agents.'

Dawson and Tyson (1936), on the other hand, made an extensive study of the relationship from many view points and came to the conclusion that ' they are intimately related and possibly different manifestations of the same pathological process.'

In view of this difference of opinion the following case may be of interest.

Case report

History. A female, aged seven-and-a-half years first complained of swelling in her left hand and fingers in December, 1940. This cleared in twenty-four hours to be followed by swelling of the left hand and wrist. Previous to this she had been lethargic and inactive and tired easily and on one occasion had complained of pains in the knees. Recently her hair had got much thinner. There was no family history of rheumatism.

Clinical findings. When the child was first seen on December 6, one week after the swelling of the left hand, her pallor and tired appearance were striking. Temperature and pulse were normal. There were no fluctuant swellings of the joints but slight diffuse enlargement of both wrists and all the proximal inter-phalangeal joints and a tendency toward ulnar deviation of the hands. No nodules were seen or felt at this time. There was some restriction of movement of the fingers and wrists. Legs, spine and neck had full range of movement and showed no swellings.

BLOOD COUNT	DIFFERENTIAL COUNT
Erythrocytes, 4,670,000 per c.mm.	Polymorphs, 58 per cent.
Haemoglobin, 92 per cent.	Eosinophils, 3 per cent.
Colour index, 0·98 per cent.	Basophils, 0 per cent.
Leucocytes, 9,000 per c.mm.	Lymphocytes, 31 per cent.
	Large monoculears, 7·5 per cent.

LYMPHATIC SYSTEM. Small glands were palpable in both groins, left axilla, occipital and right supraclavicular regions as well as the epitrochlear. The spleen was felt two fingerbreadths below the costal margin. Both tonsils were large and red and the corresponding glands enlarged. There were several carious teeth.

THE HEART was not enlarged clinically. The apex beat was in the fourth space, ½ inch inside the nipple line and 3 inches from the mid line. The first sound was followed by a soft systolic murmur at apex and base. The second

sound was normal but followed by a soft blowing mid-diastolic murmur at the apex. Sinus arrhythmia was present and the sounds varied in intensity with the respiration but the murmurs never entirely disappeared.

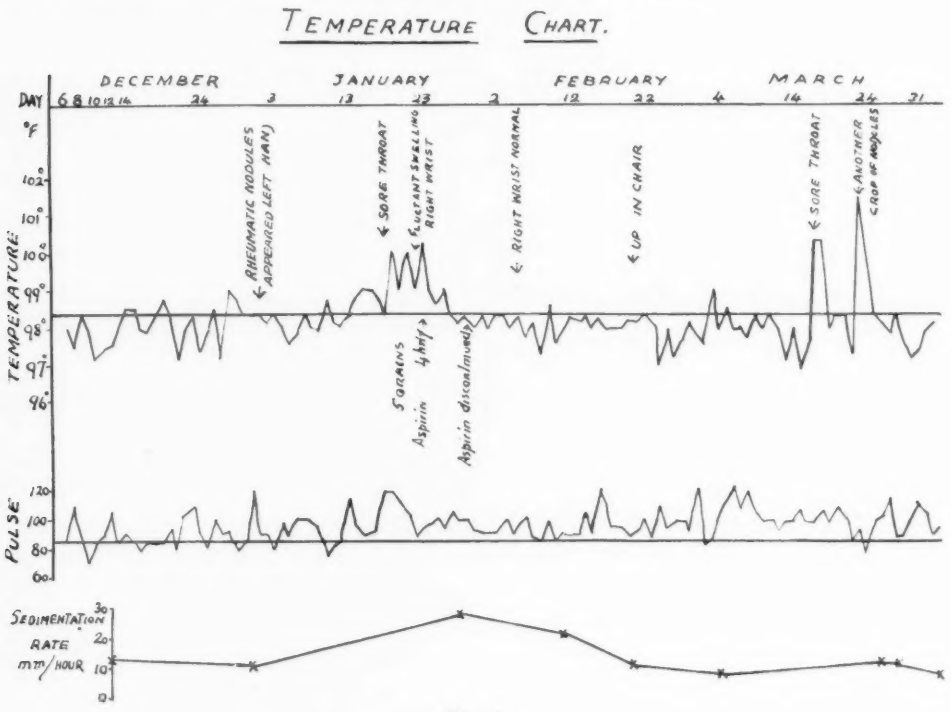

Fig. 1.

Progress. (See fig. 1 for temperature, pulse and sedimentation rate.)

Dec. 10. Four days after admission the diastolic murmur was no longer heard, although the diffuse systolic murmur persisted.

Dec. 14. Reduplication of the second sound with return of the diastolic murmur at the apex.

Dec. 17. No diastolic murmur heard.

Jan. 1. Rheumatic nodules appeared on the back of the left hand. The diastolic murmur was heard only if the child exercised to increase the rate. The spleen was much smaller.

Jan. 22. Had sore throat and temperature for last four days. The right wrist was acutely painful and swollen with fluctuation and marked limitation of movement. Throat swab grew Lancefield haemolytic streptococcus, group A.

Feb. 5. Right wrist practically returned to previous condition with slight thickening and limitation of movement.

Feb. 21. In view of the general improvement with fall of sedimentation rate to 12 mm. and rise of haemoglobin to 96 per cent. the child was allowed up. All nodules had disappeared except one on the third left knuckle (fig. 2).

March 17. Complained of headache and sore throat and vomited once. Temperature raised to 100·4° F. No joint pains but right tonsil increased in size and inflamed.

HEART. Apex beat 1 inch inside the nipple line and $2\frac{1}{2}$ inches from the mid line; that is, it had moved in half an inch. Systolic murmur still present at base and apex but no diastolic murmur heard.

March 23. Small crop of nodules appeared on second and fourth left knuckles and third right knuckle. None on legs, spine or occiput.

April 12. Tonsillectomy performed. No exacerbation of symptoms.

Fig. 2.—Left hand showing the persistent nodule proximal to the second left knuckle and remains of acute nodules on the other knuckles.

X-RAY OF HEART (March 21). Slight general enlargement with a tendency to pear-shape.

X-RAY OF WRISTS AND HANDS. Generalized osteoporosis.

X-RAY OF SINUSES. Clear.

ELECTROCARDIOGRAM. Low voltage in all leads most marked in lead 3. P–R interval normal. Left axis deviation. T waves upright in leads 1 and 2, invisible in lead 3.

Treatment. Rest with splinting of painful joints. Aspirin 5 grains four-hourly was given for seven days during the first pyrexial period with a resultant fall in temperature.

Discussion

Clinically, this is one of those uncommon cases seen in children presenting the features both of rheumatoid arthritis (the spindle-shaped fingers and enlargement of lymph glands and spleen) and of acute rheumatism (fluctuant swellings of the wrists, acute rheumatic nodules and cardiac murmurs). It is difficult to visualize the pathological condition underlying the murmurs. There are three possibilities—cardiac dilatation, endocarditis or pericarditis. A low-grade pericardial inflammation is suspected, the end result of which is not uncommonly seen at autopsy in cases of Still's disease. The pear-shaped heart, inconstant murmurs, and electrocardiogram are suggestive of this occurrence. In regard to the rheumatic nodules, there was a persistent one on the left

third knuckle such as occurs in rheumatoid arthritis, and there were two crops of acute nodules lasting only a short while, more like those seen in acute rheumatism (fig. 2). The comparatively low sedimentation rate is interesting, with a late rise after the first crop of nodules but no significant rise after the

Fig. 3.—Both hands showing the spindle-shaped fingers.

second crop. This is contrary to the usual findings in rheumatoid arthritis when the sedimentation rate is commonly maintained at a high level in active stages of the disease.

This case is presented as an example of rheumatic infection in a child combining the features of acute rheumatism and of rheumatoid arthritis.

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INFANTILE DIARRHOEA AND VOMITING

BY

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A study of the literature shows that a clinical entity under the more familiar names of gastro-enteritis or alimentary toxicosis has been recognized for many centuries as an important cause of death in the first two years of life. Certain well-defined causes of infantile diarrhoea have been determined, but there still remains a large group of cases containing a medley of types not yet clinically demarcated. According to Reuss (1936) there is among these cases no sharp division between the purely alimentary and the purely infectious types, but a continuous transition and it is therefore necessary to consider a combined alimentary-infectious aetiological complex. In the present state of knowledge the following classification of infantile diarrhoea has been adopted :—

1. SPECIFIC
   - (a) Infective, e.g. b. dysenteriae Sonne, b. dysenteriae Flexner, the typhoid-salmonella group.
   - (b) Toxic, e.g. staphylococci.
2. DUE TO LOCAL INFECTION, e.g. pelvic peritonitis. OR SYMPTOMATIC OF GENERAL DISEASES.
3. DIETETIC.
4. ALIMENTARY-INFECTIOUS COMPLEX GROUP (A.I.C. GROUP).
   - (a) Associated with parenteral infection.
   - (b) Without evidence of parenteral infection.

The A.I.C. group. The exact role of parenteral infection in any given case is difficult to assess. There is no doubt that in certain infants, infections such as cerebrospinal fever, pneumococcal pneumonia, otitis media with mastoiditis or pyelonephritis, may produce diarrhoea and vomiting and when the primary cause is effectively treated, either medically or surgically, the signs and symptoms of intestinal upset may disappear in a striking manner. On the other hand, when the demonstrable parenteral infection is a late development and presumably a complication, treatment, although advantageous, has usually little effect in comparison and the alimentary symptoms are unaffected.

Many investigators (Bessau and Bossert, 1919; Moro, 1929; Deák, 1933; Blacklock et al., 1937), have shown that in this disease, with or without clinically demonstrable parenteral infection, the upper small intestine which is normally sterile or contains only a few enterococci may harbour large numbers of coliform

organisms which have made their way upwards from the small intestine. Blacklock et al. (1937) found that in older children with parenteral infections there was also an increase in the coliform organisms in the upper small intestine, but the change was not so marked as in infants with gastro-enteritis. This seems to suggest a close relationship between parenteral infection and disturbance of alimentary function. In infants digestive processes are very unstable and physical environment as well as infection may be responsible for the disturbance of the intestine which predisposes to the altered bacteriology. The coliform organisms which gain the upper small intestine take on a pathogenic rôle in their new environment and, according to their varied fermentative and cultural characteristics, have been named dyspepsic coli by Adam (1927) or paracolon bacilli by Hassmann and Hertzmann (1934) and Reuss (1936) and Hassmann (1936). These bacilli have been shown by Goldschmidt (1931) to produce on culture outside the body a toxic substance which in small doses irritates the intestine and in larger doses actually paralyses it (Reuss, 1936; Hassmann, 1936; Deák, 1933; Hassmann and Scharfetter, 1934). These variant forms have been known to continue in the stools into convalescence when the infants have been regarded as possible carriers. Immunological investigations by Reuss (1936) and Hassmann (1936) appear to confirm the importance of these ' paracolon ' organisms in infantile diarrhoea. An exogenous genesis has been postulated by Catel (1937) in which the variant b. coli by their growth on a suitable medium outside the body produce toxic substances which after ingestion cause diarrhoea and vomiting. The intensely fatty liver which is frequently found at autopsy bears testimony to the absorption of toxins in the portal system, but the exact nature of the toxic products is open to speculation. Products of protein decomposition have been blamed, such as histamine by Boyd (1923), Finkelstein (1931) and Keller (1932), and cholin by Paffrath (1930); and others have been mentioned. Catel (1937) thinks that the irritant effects may be due to the presence of certain lower fatty acids in the upper small intestine. Although variant b. coli have been held responsible for outbreaks of gastro-enteritis, there is another aspect of the situation to be considered. As the altered intestinal bacteriology has been shown to follow parenteral infections it is, therefore, possible that some as yet unknown infection may cause outbreaks in infants in institutions. There is a form which occurs from time to time and may spread very rapidly through an open ward attacking all the susceptible infant population under two years of age. The infants affected may simply show diarrhoea with vomiting until death occurs, and the only other symptom demonstrable may be a short cough. Specimens of sputum are negative for pneumococci and streptococci and, although no current evidence can be offered, it is a clinical opinion that this is a serious and deadly form which spreads like a respiratory infection caused by a filter-passing virus.

Bessau (1935) thinks that the picture of alimentary toxicosis, with its heavy and continued loss of water and mineral salts, can only be explained on the basis of an abnormal increased permeability of the cellular membranes consequent on toxic absorption. The cells are no longer able to retain their specific contents of colloids and mineral salts and a certain interchange takes place. Thus Na and Cl ions enter the cells and substances of the K group (K, P, Mg) escape into the blood stream. Water and salt metabolism will be discussed in detail in another paper.

Present series

The five hundred and seventy-four infants in this series of cases of gastro-enteritis were admitted to the Park Hospital between January, 1937 and August, 1939. During these years two or, at times, three wards have been assigned to

infants who were certified before admission as suffering from ' zymotic enteritis,' ' gastro-enteritis,' ' diarrhoea and vomiting ' and the like. A small number was placed in individual cells, but in view of the large number treated, it was necessary to use open wards, in which these infants can be successfully nursed by adhering strictly to the details of the technique of bed isolation and liberal standards of bed spacing. The patients with diarrhoea came from their homes and from institutions such as nurseries and hospitals. The diagnosis given on admission was revised in many instances, for it was based on the clinical features only; and the cases were classified into the groups specified at the beginning of this paper. The faeces of each infant were examined on two occasions for pathogenic organisms, and when the clinical features suggested dysentery, enteric fever or a specific gastro-enteritis, the agglutination reaction of the serum was tested against organisms of the dysentery, enteric and salmonella groups. A history of any recent error in feeding leading to symptoms such as vomiting, diarrhoea, alteration in the character of the stools and loss of weight was sought, and an attempt was made to assess its bearing on the current illness. By careful examination on the day of admission and on the following day an attempt was made to detect infections or other causes of diarrhoea.

It will be clear that this series is of a mixed character since the term ' gastro-enteritis ' (or A.I.C. group) has been used for the cases of diarrhoea which remain after excluding the specific gastro-intestinal infections, local causes of diarrhoea, digestive disorders, and the parenteral infections or infectious diseases in which diarrhoea was an insignificant symptom. To give more uniformity the cases have been divided into dehydrated and non-dehydrated groups as shown in table 1, for the signs of dehydration are obvious and its presence influences adversely the severity and outcome of the illness. There were two hundred and eighty-three dehydrated infants in the series, and it is these cases which will mainly be used in a discussion of the etiology and mortality of gastro-enteritis.

TABLE 1

MORTALITY IN DEHYDRATED AND NON-DEHYDRATED CASES OF NON-SPECIFIC INFANTILE DIARRHOEA

INFANTILE DIARRHOEA (NON-SPECIFIC)	NO. OF CASES	NO. OF DEATHS	PERCENTAGE MORTALITY
All cases	574	159	27·7
Dehydrated cases	283	152	53·7
Non-dehydrated cases ..	291	7	2·4

Etiology

Age. No patient aged over two years has been seen with gastro-enteritis of the infantile type. When infants with severe gastro-enteritis were admitted from a nursery during the course of a local outbreak, children between two and five years of age came into hospital from the same institution suffering from a

mild diarrhoea which resolved on a light and mainly carbohydrate diet with gradual increase to normal feeding. Whilst these illnesses were not due to specific organisms or known dietary error, a connexion between the cases could not be proved and the value of this observation in the epidemiology of the disease must remain conjectural. Typical gastro-enteritis did not occur in children over two years of age and was less common and milder in the second year of life.

In table 2 the cases are arranged in five groups, comprising the first four trimesters and the second year for dehydrated and non-dehydrated infants. In the series 69·7 per cent. of all cases were under nine months old. The figures for dehydrated and non-dehydrated cases were 80·9 per cent. and 58·8 per cent. respectively. Infants in the second year formed 17·1 per cent. of all cases, 7·4 per cent. of dehydrated cases, and 26·5 per cent. of non-dehydrated cases. The incidence was highest between three and nine months, and above this age for the final three-monthly period of the first year there was a rapid fall to one-half the numbers in the second trimester.

TABLE 2

ANALYSIS BY AGE GROUPS

AGE IN MONTHS	ALL CASES			DEHYDRATED CASES			NON-DEHYDRATED CASES		
	NO. OF CASES	NO. OF DEATHS	PER-CENTAGE MORTALITY	NO. OF CASES	NO. OF DEATHS	PER-CENTAGE MORTALITY	NO. OF CASES	NO. OF DEATHS	PER-CENTAGE MORTALITY
0–3	109	32	29·3	61	32	52·5	48	0	—
3–6	158	56	35·4	93	54	58·1	65	2	3·1
6–9	133	47	35·3	75	47	62·7	58	0	—
9–12	76	15	19·7	33	13	39·4	43	2	4·7
12–24	98	9	9·2	21	6	28·6	77	3	3·9

Published reports show a similar picture of a disease which affects chiefly the infant under one year, but observers in Britain commonly describe the highest incidence at an earlier age. In Parsons' (1924) series most of the infants were less than three months old. Cooper (1937) found that cases were most common between three and six months, and afterwards the number affected fell rapidly. A peak in incidence between one and two months and a regular decline in frequency from the third month is described by Smellie (1939). In the present series no significant reduction in the number of cases occurred before the later age of nine months.

The percentage of the cases with dehydration in any age-group showed a parallel course which is presented in table 3 and was highest between three and six months (58·9 per cent.); it fell to lower levels between nine and twelve months (43·4 per cent.) and in the second year (21·4 per cent.). A real decrease in the severity of the illness accompanied the lessening prevalence after the eighth month of life.

TABLE 3

INCIDENCE OF DEHYDRATION IN AGE GROUPS

AGE IN MONTHS	NO. OF CASES	NO. OF DEHYDRATED CASES	PERCENTAGE OF CASES DEHYDRATED
0–3	109	61	56·0
3–6	158	93	58·9
6–9	133	75	56·4
9–12	76	33	43·4
12–24	98	21	21·4
0–24	574	283	49·3

Feeding. In this series eighteen infants or 4·5 per cent. of the infants under nine months were breast-fed at the onset of the illness, and only three of them died. The infrequency of the disease in breast-fed infants has been recognized for many years, and is further supported in recent reports on gastro-enteritis.

Findlay (1932) found 9 per cent. of the infants breast-fed in a series of three hundred cases, Cooper (1937) 3 per cent. among three hundred cases, and Smellie (1939) $2\frac{1}{2}$ per cent. in five hundred patients. Breast-fed infants according to Spence (1938) enjoy a greater freedom and enhanced recovery from disease than artificially-fed infants; and in infantile diarrhoea figures given by Smellie (1939) show that the death-rate in infants who have been breast-fed in the early months of life is as little as one-third of that in infants fed artificially from birth. The breast-fed infant is not frequently affected by the disease and is unlikely to die of uncomplicated gastro-enteritis.

Residence. The risk of infections spreading among infants living in a community such as a nursery, institution or hospital ward is well known to paediatricians; but to say that gastro-enteritis is a disease of such communities is an exaggeration, which is not supported by the present figures. One hundred and twenty-seven (22·1 per cent.) of all the cases had developed the illness in an institution, and of the two hundred and eighty-three dehydrated cases sixty-eight (24·0 per cent.) were of similar origin. No information of the populations at risk is available in order to compare the frequency of the disease in the home and institution, but it can be said that however great the likelihood of transmission of gastro-enteritis may be in communities of infants, the problem of the control and treatment of the disease in the home is the wider one. Cooper (1937) found a great increase in incidence in families of five or more, and stressed the influence of overcrowding.

Seasonal incidence. For the first quarter of this century and even longer the summer diarrhoea of infants was known as an annually recurring disease which rose to epidemic proportions in hot dry summers.

Findlay (1932) reports that in the epidemic year of 1921, 64 per cent. of the cases occurred between July and September, and in Nabarro's (1923) series of the same year the highest numbers were affected in the last two weeks of July and the first week of September. In America Marriott and others (1933) found that non-dysenteric diarrhoea in children was most frequent in the early autumn months. More recent reports show a change in the seasonal

prevalence, while they do not support the view that gastro-enteritis is now more common in winter. Almost half of Cooper's (1937) series of cases seen in Glasgow between 1931 and 1934 occurred in August, September and October, and 68·8 per cent. from June to October. Smellie (1939) regarded the slight increase in incidence from July to October in his series as insignificant, and considered that the summer diarrhoea of text-books has been replaced by a disease of mixed etiology which is present throughout the year.

The figures for the years 1937 and 1938, which are the completed years in the present series, are shown in the tables. Cases seen in 1939 have been excluded because the period until August only has been analysed; later in the year the rate of admission of patients was altered by a reduction in the available beds and by evacuation of infants as well as by a decline in the incidence of enteritis, which is suggested by the fall in the weekly number of deaths from this cause in the later months of 1939. The cases are grouped in the month of onset of the illness, and table 4 presents the results for all cases seen in the two years. Table 5 deals with dehydrated cases and those without parenteral infections on admission have been analysed in table 6.

TABLE 4

INCIDENCE OF CASES AND DEATHS IN YEARS 1937 AND 1938 GROUPED BY MONTH OF ONSET OF SYMPTOMS

MONTH	NO. OF CASES	PER-CENTAGE OF TOTAL	NO. OF DEATHS	PER-CENTAGE DEATH RATE	MONTH	NO. OF CASES	PER-CENTAGE OF TOTAL	NO. OF DEATHS	PER-CENTAGE DEATH RATE
January	17	3·8	4	23·5	July ..	53	11·9	17	32·1
February	39	8·8	4	10·3	August ..	43	9·7	10	23·3
March ..	20	4·5	7	35·0	September	53	11·9	17	32·1
April ..	31	7·0	11	35·5	October ..	43	9·7	5	11·5
May ..	35	7·9	10	28·6	November	29	6·5	7	24·1
June ..	40	9·1	14	35·0	December	41	9·2	14	34·1

444 cases; 120 deaths.

TABLE 5

MONTHLY INCIDENCE AND DEATH RATE IN 211 DEHYDRATED CASES (YEARS 1937 AND 1938)

MONTH	NO. OF CASES	PER-CENTAGE OF TOTAL	NO. OF DEATHS	PER-CENTAGE DEATH RATE	MONTH	NO. OF CASES	PER-CENTAGE OF TOTAL	NO. OF DEATHS	PER-CENTAGE DEATH RATE
January	5	2·6	4	80·0	July ..	24	11·4	17	70·8
February	7	3·3	3	42·9	August ..	23	10·9	10	43·5
March ..	10	4·7	7	70·0	September	33	15·6	17	51·5
April ..	19	9·0	11	57·9	October ..	21	10·0	5	23·8
May ..	13	6·2	10	76·9	November	15	7·1	7	46·7
June ..	17	8·1	13	76·5	December	24	11·4	13	54·2

211 cases; 117 deaths.

TABLE 6

MONTHLY INCIDENCE IN 1937 AND 1938 IN CASES WITHOUT INFECTIONS ON ADMISSION

MONTH	ALL CASES	DEHYDRATED CASES	MONTH	ALL CASES	DEHYDRATED CASES
January ..	9	3	July	43	21
February ..	23	3	August ..	30	17
March	17	10	September ..	40	25
April	25	16	October ..	37	20
May	25	11	November ..	17	8
June	33	16	December ..	18	12

317 cases; 162 dehydrated.

Of the four hundred and forty-four cases more than half (52·3 per cent.) occurred in the five months from June to October. The highest number of cases was in July and September and the lowest in January and March, whilst in the other months the variation in the figures was small. The analysis of the two hundred and eleven dehydrated cases gives similar results; 56 per cent. occurred in the same five months, and the highest incidence was in September and the lowest in January and February. It is noteworthy that July and December had the same number of cases, which was exceeded only in September.

Since gastro-enteritis may be a disease of mixed causation, it might be thought that the seasonal incidence of any series of cases would be the result of the interplay of a variety of infections of different epidemic constitution. Cases without parenteral infections early in the illness have been analysed in order to see if they have a different seasonal incidence from the whole group; since respiratory infections such as bronchitis, bronchopneumonia and otitis media are more common in winter, it was thought that a more marked seasonal increase in the summer months might be seen when the patients in whom gastro-enteritis and a parenteral infection were associated early in the illness were excluded from the series. Table 6 does not show any wide divergence from the incidence in the previous tables. In the five months from June to October a slight increase in the percentage of cases occurred especially among the dehydrated infants; the figures were 57·7 per cent. for all cases and 66·0 per cent. for dehydrated cases. An alteration of some note is that the incidence in December was lowered, being less than half that in July. In gastro-enteritis unassociated with parenteral infections there was a greater tendency to assume epidemic increase in summer and autumn and to maintain a lower incidence without peaks in the other seasons of the year.

Parenteral infections. Infections in systems other than the gastro-intestinal tract are frequently found in infants with gastro-enteritis, but only the parenteral infections which appear in the early days of the illness can be regarded as playing a part in causing the disease. An attempt has been made to detect all of these conditions by a full examination of the infant, including inspection of the ear-

drums, on the day of admission and the following day. A catheter specimen of urine was examined when symptoms such as fever, vomiting and meningism indicated the probable presence of an infection of the urinary tract.

One hundred and seventy-five (30·5 per cent.) of the five hundred and seventy-four infants had one or more parenteral infections on admission to hospital, and of the two hundred and eighty-three dehydrated cases seventy-four (28·1 per cent.) can be placed in the same group. Even if these parenteral infections acted as causal agents in every instance, less than one-third of the cases could be attributed to this source. Smellie (1939) found that 46·2 per cent. of his patients had unequivocal signs of parenteral infection on admission to hospital. Over half of these infections in Smellie's series were otitis media and mastoiditis, while among the present cases there was a much lower frequency of otitis and mastoiditis, which formed only 13·2 per cent. of the infections in all patients and 19·0 per cent. in the dehydrated cases. The great difference in the incidence of disease of the middle ear accounts for the significant variation in the percentage of cases with parenteral infections early in the illness in these series seen in different parts of Britain during approximately the same years.

The nature of these conditions is shown in tables 7 and 8. The figures for all cases and dehydrated cases were similar. Infections of the respiratory tract such as otitis media, mastoiditis, stomatitis, pharyngitis, laryngitis, bronchitis and bronchopneumonia formed 78·9 per cent. of the accompanying diseases in all cases and 81·4 per cent. in the dehydrated cases. Other infections were present only in a small number of cases. Four-fifths of the infections which occurred early in the course of gastro-enteritis in this series involved the respiratory tract, including the middle ear and mastoid.

TABLE 7

NATURE OF PARENTERAL INFECTIONS PRESENT ON ADMISSION

PARENTERAL INFECTIONS	NO. OF CASES	PERCENTAGE OF TOTAL	NO. OF DEATHS	PERCENTAGE MORTALITY
Otitis media and mastoiditis	14	8·0	1	7·1
Tonsillitis, laryngitis, bronchitis and bronchopneumonia	96	54·9	21	21·9
Urinary infections	7	4·0	2	28·6
Stomatitis	10	5·7	3	30·0
Eczema or dermatitis	17	9·7	2	11·8
Congenital syphilis	1	0·6	1	100·0
Vaccinia	4	2·3	1	25·0
Measles	1	0·6	1	100·0
Whooping cough	7	4·0	1	14·3
Bronchitis and otitis media	7	4·0	3	42·9
Bronchitis and urinary infections	3	1·7	1	33·3
Bronchitis and stomatitis	3	1·7	1	33·3
Bronchitis and dermatitis	2	1·1	2	100·0
Urinary infection and stomatitis	1	0·6	1	100·0
Otitis media and dermatitis	1	0·6	0	0
Bronchitis, otitis media and stomatitis	1	0·6	0	0
Total	175	—	41	23·4

TABLE 8

NATURE OF PARENTERAL INFECTIONS PRESENT ON ADMISSION IN 74 DEHYDRATED CASES

PARENTERAL INFECTIONS	NO. OF CASES	PERCENTAGE OF TOTAL	NO. OF DEATHS	PERCENTAGE MORTALITY
Otitis media or mastoiditis	7	9·5	1	14·3
Laryngitis, bronchitis and pneumonia	33	44·6	18	54·6
Urinary infections	5	6·8	2	40·0
Stomatitis	5	6·8	3	60·0
Eczema and dermatitis	4	5·4	1	25·0
Congenital syphilis	1	1·4	1	100·0
Vaccinia	1	1·4	1	100·0
Measles	1	1·4	1	100·0
Whooping cough	2	2·7	1	50·0
Bronchitis and otitis media	6	8·1	3	50·0
Bronchitis and urinary infections	3	4·1	1	33·3
Bronchitis and stomatitis	2	2·7	1	50·0
Bronchitis and dermatitis	2	2·7	2	100·0
Urinary infection and stomatitis	1	1·4	1	100·0
Otitis media, bronchitis and stomatitis	1	1·4	0	—
Total	74	—	37	50·0

Otitis media and mastoiditis were less common in the present series than in others of which reports have been published and around which controversy has developed on the rôle of middle-ear disease in the causation of gastro-enteritis.

For example, the percentage of the cases showing otitis or mastoiditis was as high as 25 per cent. in Smellie's (1939) series and 26 per cent. in Cooper's (1937) cases, whereas only 5 per cent. of the cases now reported suffered from these conditions. Findlay (1932) expressed doubts about there being a causal relationship between otitis media and gastro-enteritis, but observations indicating an etiological connexion between these diseases have been recorded by several observers (Floyd, 1925; Marriott, 1928; Ebbs, 1937; and McConkey and Couper, 1938) on a wide range of clinical and post-mortem material. Smellie (1939) thinks that parenteral infection (especially disease of the middle ear) is sometimes the cause and sometimes the consequence of infantile diarrhoea.

This opinion must be accepted, but the proportion of cases due to parenteral infections must be regarded as variable. Whilst infections of the middle ear, bronchial tree and lungs form the greater part of these conditions, there are local and seasonal differences in their relative importance. Otitis media was found much less often than chest infections in the present series. These divergences in the frequency of the different infections may depend on the interplay of such factors as climate, season and variation in the prevalence and virulence of the haemolytic streptococcus. Many of the parenteral infections were mild and would not in themselves be a cause of severe illness; and even if it is accepted that such minor infections play a causal rôle in gastro-enteritis, they can act only as trigger mechanisms on the basis of a constitutional abnormality or gastro-intestinal imbalance of infancy.

Mortality

The average death rate in this series was 27·7 per cent. A striking difference is seen in table 1 between the death rate in the two hundred and eighty-three dehydrated infants (53·7 per cent.) and in the two hundred and ninety-one non-dehydrated infants (2·4 per cent.), and this remarkable disparity indicates how important it is to assess correctly the state of the water balance in these sick infants. Many of the non-dehydrated patients may have suffered from diarrhoea due to a digestive upset, for dietetic errors are difficult to detect, but this error is less probable in the dehydrated cases. If the term gastro-enteritis is confined to the severer cases of diarrhoea which show dehydration, cyanosis or toxicity, the clinical syndrome is more sharply defined, although the individual element in detecting dehydration will influence the mortality rates in the series of different observers.

Cooper (1937) had a death rate of 47·2 per cent. in a series of three hundred patients, of whom 66·8 per cent. were dehydrated. A death rate of 48 per cent. was recorded by Smellie (1939). These figures are of the same order as the mortality rate of 53·7 per cent. among the dehydrated infants in this series. Lower death rates which have been described by other observers such as Cohen (1933) may be due to inclusion of milder cases of gastro-enteritis in the series.

In comparing the effect of certain factors on mortality rates attention will be paid mainly to the dehydrated cases.

Age. The figures in table 2 show that the disease was most fatal under nine months of age. In the three monthly periods under nine months the death rates were 52·5 per cent., 58·1 per cent. and 62·7 per cent. respectively for the dehydrated cases. There was a sharp fall to 39·4 per cent. between nine and twelve months and in the second year this decline in the mortality continued to 28·6 per cent., which was less than half the highest percentage between three and nine months. Too few infants under one month were seen to give figures for the neonatal period, in which Cooper (1937) found a high mortality of 73·6 per cent. It may be concluded that under nine months over half of the affected infants will die and even above this age death is a probable issue in one-third of the patients.

Duration of symptoms. The results in one hundred and sixty-eight cases which were treated by constant subcutaneous fluid have been analysed according to the day of illness on admission in table 9. There is little difference in mortality between the infants who had been ill for not more than three days and others whose symptoms were of four to six days' duration; when the symptoms had been present for seven days or longer there was a definite decrease in the death rate. Under the age of nine months the duration of symptoms had no definite influence on the death rate. In infants over nine months old the proportion with symptoms of seven or more days' duration was increased because of the lessening severity of the disease. The period of the illness at which treatment was begun did not affect the outcome in this analysis, but an examination by individual days over a large series would be required to decide whether early treatment improves the prognosis.

TABLE 9

EFFECT OF DURATION OF ILLNESS BEFORE ADMISSION ON DEATH RATE IN 168 CASES TREATED MAINLY BY CONSTANT SUBCUTANEOUS DRIP

AGE IN MONTHS	1 TO 3 DAYS		4 TO 6 DAYS		7 DAYS OR MORE	
	NO. OF CASES	NO. OF DEATHS	NO. OF CASES	NO. OF DEATHS	NO. OF CASES	NO. OF DEATHS
0–3	24	11	8	4	10	6
3–6	21	12	22	14	9	3
6–9	14	7	18	9	10	5
9–12	6	2	4	2	12	3
12–24	4	2	2	1	4	0
0–24	69	34 (49·3)	54	30 (55·6)	45	17 (37·8)
0–9	59	30 (50·8)	48	27 (56·3)	29	14 (48·3)
9–24	10	4 (40)	6	3 (50)	16	3 (18·8)

Six of the 174 cases in table were excluded because of an inadequate history of symptoms. Figures in brackets represent percentages.

Season. Among the dehydrated cases shown in table 5 the death rate was high throughout the year except in the month of October, and the highest percentages in January and March of the winter months and May, June and July of the summer months differed little.

Parenteral infections. Table 10 presents a comparison of the death rates in the two hundred and eighty-three dehydrated cases with and without parenteral infections on admission. Fifty per cent. of infants with parenteral infections died, while death occurred in 55 per cent. of the cases showing no infections. Under six months of age, however, the mortality rate was higher among the infants with parenteral infections, but at later ages a lower fatality rate was uniformly present in this group. Thus the cases of gastro-enteritis

TABLE 10

ANALYSIS OF THE 283 DEHYDRATED CASES IN AGE GROUPS ACCORDING TO THE PRESENCE OR ABSENCE OF PARENTERAL INFECTION ON ADMISSION

AGE IN MONTHS	ALL CASES			PARENTERAL			NON-PARENTERAL		
	NO. OF CASES	NO. OF DEATHS	PER-CENTAGE MOR-TALITY	NO. OF CASES	NO. OF DEATHS	PER-CENTAGE MOR-TALITY	NO. OF CASES	NO. OF DEATHS	PER-CENTAGE MOR-TALITY
0–3	61	32	52·5	10	6	60·0	51	26	51·0
3–6	93	54	58·1	20	15	75·0	73	39	53·4
6–9	75	47	62·7	25	12	48·0	50	35	70·0
9–12	33	13	39·4	11	2	18·2	22	11	50·0
12–24	21	6	28·6	8	2	25·0	13	4	30·8
0–24	283	152	53·7	74	37	50·0	209	115	55·0

which may have been caused by infections outside the gastro-intestinal tract had a death rate which was higher than the mortality in cases of other origin only among infants less than six months old; and, indeed, at the later ages the prognosis in the parenteral cases was slightly more favourable than in the whole dehydrated group. Cooper (1937) reported that in his cases the results of the illness were not strikingly affected by parenteral infections, and that otitis media had not adversely influenced the outlook. In table 8 it is evident that the infections associated with a high mortality were bronchitis and broncho-pneumonia, urinary infections and stomatitis. The death rate in infants with otitis media and mastoiditis was much below the average level and, even when instances of otitis media in patients with more than one parenteral infection were included, it amounted to only 28·6 per cent. in the dehydrated cases.

Only the infections already present on admission have so far been considered. Gastro-enteritis was in seventy-four of the two hundred and eighty-three dehydrated infants complicated by parenteral infections at this time and another fifty-eight patients developed a complication of this kind after admission to hospital. The nature of the infections and the death rate in the fifty-eight cases are set forth in table 11. Twenty-six of them (48·8 per cent.) died. One hundred and thirty-two (46·6 per cent.) of the dehydrated infants with gastro-enteritis had a parenteral infection at some stage of the illness and death occurred in sixty-three of the number (47·7 per cent.), a percentage which is lower than the average mortality rate of 53·7 per cent. Infections of the respiratory tract remained the most fatal of the complications, and diseases of the middle ear and mastoid were more prominent and were associated with a higher death rate in the smaller group, in which it complicated the gastro-enteritis, than in the infants in whom otitis media and mastoiditis were a presenting feature.

TABLE 11

PARENTERAL INFECTIONS AFTER ADMISSION TO HOSPITAL

PARENTERAL INFECTIONS	DEHYDRATED CASES		ALL CASES	
	NO. OF CASES	NO. OF DEATHS	NO. OF CASES	NO. OF DEATHS
Otitis media	11	5	14	5
Rhinitis, bronchitis and broncho-pneumonia	31	14	45	14
Urinary infections	0	0	3	1
Stomatitis	2	1	2	1
Eczema, boils and dermatitis	2	0	4	0
Pertussis	5	2	6	2
Submaxillary adenitis	1	1	1	1
Staphylococcal pyaemia	1	1	1	1
Otitis media and bronchitis	3	2	5	2
Otitis media and pertussis	1	0	1	0
Stomatitis and eczema	1	0	1	0
Total	58	26	83	27

Whether the parenteral infections were present as a causal factor or developed during the course of the illness, they had no adverse influence on the mortality rate. Bronchitis and bronchopneumonia were the most common of the infections and occurred in the majority of the fatal illnesses. The importance assigned to otitis media and mastoiditis by several observers cannot be confirmed; in the series only twenty-five out of the one hundred and thirty-two cases with parenteral infections had these conditions and the nine deaths among these patients imply a death rate of 36 per cent., which is lower than the average level for the dehydrated infants whether with or without parenteral infections.

Treatment

Prophylaxis. Breast-feeding from birth is almost a sure guarantee that the infant will not succumb to infantile diarrhoea and vomiting and when diarrhoea supervenes it generally signifies digestive upset, parenteral infection or specific infection. When this occurs, it is imperative that breast milk be continued and it is, therefore, a mistake of judgment to deprive the child of the mother's milk. Treatment is best carried out at home if the mother is unable to feed her child in hospital. In spite of the undoubted safeguard provided by breast-feeding, it has been estimated that only 30 per cent. of mothers at the present time completely feed their infants for the first six months of life, and it is certain this percentage will drop still lower as the rigours of war upset the conditions of home life.

Parenteral infection. A complete clinical examination must be carried out as soon as possible after admission, but this must be done in a warm atmosphere, preferably in front of a fire. With the good results from chemotherapy in several infections the importance of early treatment cannot be too strongly stressed. Details of treatment follow modern accepted teaching.

Feeding. A starvation period of 24 to 48 hours is a good routine, but severely dehydrated and toxic infants will benefit from an even longer period. During this time water should be given by mouth in small amounts at frequent intervals and if parenteral fluid is not being given concurrently, half-normal saline should also be given by mouth. Lelong (1938) and other French authors prefer to give vegetable soups and cereal concoctions, but the value of the latter is mainly due to their salt content in some palatable form. This regime leads to such a marked improvement in toxic cases that it would appear desirable to prolong the starvation period for a much longer period if a more satisfactory method of parenteral feeding could be evolved. Some attempts in this direction will be described later. Glucose is next added to alternate feeds. At this stage many authors favour a milk-free transition diet. Thus Czerny and Keller (1928) recommend the use of whey with, later, the addition of a 10 per cent. rice gruel, but it has generally been possible by careful and gradual change to pass from glucose and water to a separated dried milk using small feeds at regular intervals with modifications as dictated by progress. If vomiting has ceased, the character of the stools has improved, and the weight is more or less constant, the next step is the gradual replacement measure by measure of the

separated by half-cream dried milk. In general, all infants with gastro-enteritis tolerate fats badly and too sudden increase of fat in the feeds will invariably precipitate a relapse of the diarrhoea. When the infant is taking adequate amounts of half-cream dried milk, it is advisable in convalescence to give extra iron in the form of the ferrous sulphate syrup advised by Mackay (1937). When the acute symptoms have subsided and the stools returned to normal, daily amounts of the concentrated vitamin preparations should also be given and continued for some time afterwards.

The most difficult and the most disappointing patients are those with persistent vomiting without any causative parenteral infection. When there is marked acidosis and large amounts of fluids have been given parenterally without abatement of vomiting, it is usually found that other measures, such as the giving of sodium bicarbonate, are only temporary expedients and if the vomit contains coffee ground material the prognosis is almost invariably fatal. The giving of milk in any form to these patients results in an exacerbation of symptoms. It is almost impossible to get nourishment by the mouth absorbed, and the slow but continuous wasting is soon fatal. The use of acid milk feedings goes back to antiquity to the days when Herodat recommended sour milk in the treatment of diarrhoea. Buttermilk has also been used in various countries for several centuries and good results have been reported following the use of commercial preparations by Langstein (1927), Engel (1930), Feer (1934), Glanzmann (1934) and Studer (1935). The power of precipitation of casein curds in finely divided form and the low fat, high calcium content of these foods are therapeutic advantages, but it is almost generally agreed that as stated by Marriott (1927) and Feer (1934) the value is chiefly in the lactic acid content and is not due to any specific action of the lactic acid bacilli.

Marriott (1935) and Freudenberg (1929) think that the acidification of the milk causes neutralization of a portion of buffer substances so that the acidity attained in the stomach approximates to that when human milk is fed. This acidity is sufficient to inhibit the growth of paracolon bacilli as demonstrated by Hassmann (1936) whose experimental work appears to justify the use of acid milks as prophylactic agents to prevent exogenous paracolon bacilli infection.

The results, however, from acid milk feeding in treatment, have not been better than those with ordinary dried milk.

The apple diet was first introduced by Moro (1929) and Heisler (1929) and since then various authors have reported such widely divergent results that this form of treatment has been relegated to the background only to be revived by enthusiasts from time to time. Finely divided apple and a commercial preparation have been used in the present series, but no improvement following their use in young infants has been noticed. In older infants, however, over nine months of age, with a sub-acute form of illness and capricious appetite, the commercial preparation is a useful diet when ringing the changes, and from time to time an infant is met with who prefers it to dried milk. It is interesting to note that Voss (1937) has demonstrated by x-ray examination that the reaction of the intestine to apple diet in infants in the first six months of life is strikingly different

from that in older infants and children. Pectin and cellulose are the elements reputed to be of specific value, and recently Howard and Tompkins (1940) have reported excellent results using a standard pectin agar milk mixture. Their chief success was in the treatment of a rather unusual epidemic of diarrhoea with mucus and blood in the stools in a group of twenty-three newly born infants, from the faeces of whom no known pathogenic organisms were isolated. This latter treatment was also successfully applied in a group of older infants and children.

Parenteral fluid therapy. This will be discussed in a later communication when the question of water and salt metabolism is reviewed in detail. Suffice it to say that at present the continuous subcutaneous route for dehydrated cases is favoured, ringing the changes between normal saline, Ringer's solution and 3 per cent. glucose in 0·25 per cent. saline, and in severely ill patients this should be supplemented in the first twenty-four hours by intraperitoneal or intravenous therapy.

Blood transfusion. Marriott (1927) believed that beneficial effects of parenteral fluid therapy were more lasting if combined with blood transfusion. Blood was found only of value in the present series in patients with a definite anaemia and in those with a long-standing infection, such as otitis media. Plasma transfusions as recommended by Aldridge (1938) are valuable in the later stages of the illness when there is hypoproteinaemia, either with or without oedema. When the serum protein is maintained at a normal level parenteral fluid therapy by the continuous subcutaneous route can be maintained. Blood transfusions are, therefore, chiefly of value in the rather older infants, approximately nine months of age and over, as they appear to tide the child over the danger period till it reaches an age when the body powers of recovery appear to be better developed.

Drugs. Apart from the chemotherapy of certain parenteral infections, drugs are of little value in treatment. Aperients are of value in a limited number of cases in which food poisoning is suspected, but are of little value in any case after the first twenty-four hours of the illness. Alcohol has its advocates but Keller (1932), and others think it is contra-indicated. In the present series brandy in 20 to 30-minim doses has been used several times a day, as it has been found of value as a stomach sedative in certain cases in which there was difficulty in feeding and recurrent vomiting. It is of no value when vomiting is persistent and intractable and associated with gross metabolic disturbance. Nepenthe, also, has been used when there was persistent restlessness and resultant loss of sleep, but these symptoms are of evil import and usually signify a fatal issue.

Parenteral alimentation. Present methods of treatment are designed to combat dehydration by the use of various salt solutions and water, but the greatest proportion of the caloric food intake is still given by mouth to be absorbed from the alimentary tract under adverse conditions. Broadly speaking, to sustain life six elements must be supplied—water, salts, carbohydrate, protein, fat and vitamins. The first three have been used extensively in treatment and certain vitamins (B_1, B_2, C and nicotinic acid) can also be given, but so far suitable solutions of protein and fat have still to be found. Human

plasma transfusions are the best means available of replacing depleted serum protein and their value is undoubted when hypoproteinaemia with or without oedema is present, but plasma protein has the drawback that it must first be hydrolysed in the body into its constituent amino-acids before it can be of any value as a source of tissue protein, and it is very doubtful if this process can occur in a severely ill child. Of the twenty odd amino-acids which make up protein foods, only nine, and possibly ten, are essential.

Rose (1937) has calculated the ideal formula of essential amino-acids for growth, but it is a practical impossibility to prepare each of these essential amino-acids separately and mix them in the right proportions. A much more economical method is to select a relatively pure protein like casein which when hydrolysed produces all the essential amino-acids except tryptophane, which is almost completely destroyed in the process. This mixture also contains relatively little cystine. In animals it has been found that a 10 per cent. hydrolysate of casein to which has been added 2 per cent. tryptophane and 2 per cent. cystine can be used parenterally to maintain the nitrogen balance. This solution has been well tolerated also by man when given intravenously, by Elman and Weiner (1939) with either Ringer's solution or dextrose solution. Experimental and clinical studies by Elman and Weiner (1939) have shown that the injected amino-acids are rapidly utilized leading to the regeneration of serum protein and the reduction of nutritional oedema.

In the present series a dilute isotonic solution has been used and found to be satisfactorily absorbed by the subcutaneous route without any apparent ill effects. Unfortunately, however, as the treatment is necessarily prolonged and the cost of preparation of tryptophane is still high, the cost of undertaking an extensive investigation was found to be prohibitive. Amino-acid therapy must therefore wait until a more economical method of preparation has been discovered. From the viewpoint of caloric intake the advantage of giving fat is obvious and actually a fine emulsion for intravenous injection has already been prepared by Holt et al. (1935); it is doubtful, however, if it is really necessary for maintenance. It has also been found that, even for growth, fat is dispensable if one unsaturated fatty acid—linoleic acid—is provided, as the other necessary lipoids can be manufactured from protein and carbohydrate. By developing a natural balanced and economic form of parenteral alimentation, the beneficial effects of starvation treatment can be prolonged to give rest to the alimentary tract. The best results from present methods of treatment mean recovery in only half the dehydrated infants, but in a proportion of the others there develops after several weeks a characteristic picture of starvation combined with toxaemia leading to an ' old man ' appearance; it is therefore hoped that new methods of treatment along the lines suggested will lead to a reduction in infant mortality from the disease.

Other measures. Stomach lavage is always worth a trial in cases of persistent vomiting, but the benefit is usually only temporary and once the vomit has reached the coffee ground stage, lavage produces little if any clinical improvement.

Colonic lavage with warm saline solution has a definite place in treatment when the stools are frequent, watery and so acid in character that excoriation of the buttocks is liable to occur.

Ward management

The only guides in dealing with the management of isolation are based on empirical knowledge of gastro-enteritis and inexact analogy with other infections of which experience is securely founded. Measures designed to control the spread of infection should aim at eliminating the transmission of pathogenic organisms of intestinal origin and bacteria or viruses from the respiratory tract in droplets; in open wards the conditions should be such as to prevent aerial carriage of pathogenic bacteria and viruses, which has been established as a factor in the spread of infection by the work of Wells and Wells (1936) and Cruickshank (1939). Individual cells or chambers in association with an open ward or the Hiorns ward (described by Brincker, 1938) provide the necessary isolation with reasonable economy of staff and beds. For various reasons this may not be practicable; and an open ward can be used with little risk of spread of enteritis or relapses but with a high rate of complications. Relapses or fresh attacks of severe enteritis were seen on three occasions when there were too many acute cases in the ward; complications developed after admission in about one-fifth of the dehydrated cases. Bed isolation should prevent indirect transmission and much can be done to reduce droplet infection or aerial carriage by free ventilation, damp or vacuum cleaning, and careful disposal of soiled linen.

The ratio of nurses to infants was four to seven in the ward described by Smellie (1939). In the present series eight nurses were available in a sixteen-bedded ward and the number increased by one or two when occasion arose. The infant with enteritis requires frequent attention throughout the day and night and hours of duty by day and night have to meet this need; in practice one nurse can attend to four to six infants according to the severity of the illness. Dilution of the ward with older infants suffering from gastro-enteritis and convalescent cases lessens the work of nursing and diminishes the risk of cross-infection; four or five acute cases in a sixteen-bedded ward is a safe limit, ensuring against relapses and overworking of the staff. A system of 'feeders' and 'changers' is preferable, and essential if the nurses are not experienced in isolation methods. It is estimated that separation of 'feeding' and 'changing' increases the requirement of nurses by one-third. When this system cannot be adopted, one nurse should attend to the preparation of the feeds whether they are done daily or by single feeds and should not engage in 'changing.'

The ward temperature requires to be maintained and free ventilation across the ward secured. The standard of twelve feet between the bed centres is necessary for spacing. Attendants or visitors with acute infections should be excluded from the ward. Masks were adopted at seasons when acute illnesses were prevalent among the nurses; the envelope type can be worn at work for long periods. Daily weighing of the infants in the acute phase and accurate records of the fluid intake, stools and vomits give valuable information.

Destructible squares are convenient and should be used in the acute period of the diarrhoea. Later a small square of lint or gamgee inside the napkin is convenient. Bins on movable stands should be used to receive and dispose of

destructible squares or any dressings to the buttocks, and separate bags should be used for ordinary squares and linen. Clean squares and linen should be kept covered and handled only by a ' clean ' nurse. Sluicing is the duty of ' changers,' but it is better that the ward staff should not do sluicing, and dispose of the bags to a central sluice-room or ' foul washer ' for separate treatment. Bathing is confined to convalescents, but as convalescent carriers of paracolon bacilli have been described the possibility of conveying infection by bath water should be foreseen by providing individual baths. A refrigerator is required for the feeds. Detailed rules are necessary to establish a technique of bed isolation. As far as possible the acute cases can be put in the isolation rooms attached to an open ward.

Summary

The etiology of infantile diarrhoea and vomiting is discussed and a simple classification given.

In the series of five hundred and seventy-four cases of gastro-enteritis (A.I.C. group) there was a death rate of 27·7 per cent. The greater proportion of the patients contracted the disease at home and only about 20 per cent. of the total number were admitted from institutions. Although cases were admitted throughout the year, the demand for beds was greater in summer and autumn. On admission there was evidence of parenteral infection in less than one-third of the total number and approximately four-fifths of these showed involvement of the respiratory tract. Infections of the middle ear and mastoid accounted for a relatively smaller proportion of the total respiratory infections than has been noted by other observers. Taking the series as a whole, parenteral infection had no apparent effect on the general death rate. Age seems the most important feature in prognosis as the great majority of the deaths occur in infants less than nine months of age.

Whilst the general nursing management must be of a high order to ensure success with consistently good results, the most important single factor in treatment is the relief of dehydration. The value of constant subcutaneous infusions, supplemented in severe cases by fluid given either by the intraperitoneal or intravenous route is important. The death rate in two hundred and eighty-three dehydrated cases—53 per cent.—is in marked contrast to that in two hundred and ninety-one non-dehydrated cases—2·4 per cent.—and serves to emphasize the great importance of a careful assessment of the water balance in these infants.

Some notes on intravenous alimentation are recorded.

Management in open wards is possible only if there is adequate bed spacing, proper dilution of cases and if a strict nursing technique on the ' barrier ' or ' bed ' isolation method is rigorously enforced. Individual isolation accommodation is the ideal method.

The great prophylactic value of breast-feeding is again demonstrated and it can confidently be asserted that if a properly breast-fed infant is protected from parenteral infection, the danger to life from infantile diarrhoea and vomiting is negligible.

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SHOCK IN THE NEWBORN INFANT

BY

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At the present day physicians and surgeons are more anxious than ever to understand the mechanism of shock, to estimate its gravity and to supply adequate treatment. Moon (1938) defined the condition as a circulatory deficiency, neither cardiac nor vasomotor in origin, characterized by a decrease in blood volume, a haemoconcentration and a fall in cardiac output. Beside these findings numerous other changes frequently occur; a tachycardia, a reduction in blood pressure, an initial rise in blood sugar followed by a rise in non-protein nitrogen and a fall in serum proteins, and lastly a fall of serum sodium and rise of the potassium. The behaviour of the chlorides is variable for there is probably a chloride shift as shown by the presence of a hypochloraemia in the serum and a hyperchloraemia in the blood corpuscles in cases of severe shock. It will now be shown that both the mother and her infant at the time of parturition frequently exhibit the above features no matter whether clinical shock is present or not.

Before giving an account of the present investigations on the blood chemistry, it is necessary to explain the omission of a record of the heart rate, blood pressure and the degree of haemocentration. The pulse rate is an unreliable guide to the presence of shock, for as McMichael (1941) points out the pulse rate in adults does not necessarily accelerate with the onset of shock, and if it should do so, it seldom exceeds 120 beats per minute irrespective of the gravity of the patient's condition. Similarly, in the newborn infant, the heart rate and in addition the blood pressure are of little value in detecting shock; in fact, such observations may be deceptive. For example, accurate determinations of the blood pressure are extremely difficult and the infant's pressure is raised by an unusual amount of trauma in the birth passages or hypertension in the mother (Rocker and Connell, 1924; Abt and Feingold, 1930; Reis and Chaloupha, 1923; Brown, 1933; and Woodbury et al., 1938). With regard to haemoconcentration, Moon (1938) states that it occurs before changes take place in the blood chemistry and that it is most easily determined by repeatedly enumerating the number of red cells per c.mm. of blood, or by estimating the haemoglobin content of the blood at intervals and comparing the results. In the newborn infant such results are open to criticism since the activity of the bone marrow is great and is liable to fluctuate considerably while the infant adapts itself to its new surroundings. In addition, the physiological haemolysis of the red

cells at birth will also render haemoconcentration values inaccurate. Nevertheless, it is generally accepted that haemoconcentration does occur during the first three-and-a-half to forty-eight hours after birth, as the red cell count rises during this period (Lucas, 1921; Lippman, 1924; Merrit and Davidson, 1933; Konzelmann, 1934; and Rasi and Bollet, 1938), and subsequently falls. Therefore, a more reliable method of estimating shock must be sought.

Method of investigation

Details of the mother's age, pregnancies and health during the last pregnancy were taken. The details of the labour with special reference to the taking of fluid or food, the type of delivery and the duration of the labour were recorded. If the presentation of the infant was an occipito-anterior and birth occurred without the aid of instruments it was termed a spontaneous delivery, but if forceps were applied to the head the fact was indicated on the accompanying charts. Breech extractions and babies born by caesarian section have also been investigated. The type of anaesthetic given was light chloroform anaesthesia for all normal cases while the head of the infant was being born, but deep and prolonged anaesthesia was required for all instrumental and some breech deliveries. For mothers undergoing caesarian section, gas, oxygen and ether were administered. The above details on anaesthetics have not been charted, but in two cases information regarding twilight sleep and local anaesthesia which were used instead of the routine procedure have been recorded on the charts. Points of interest in the history of the foetus were abnormal foetal heart sounds and the presence of meconium in the liquor amnii, which have been interpreted as a sign of foetal distress. In order to assess the infant's vitality at birth, particular attention was paid to its colour, muscle tone, onset and character of respirations, and general behaviour. Caput succedaneum and moulding of the cranial bones were also looked for. Later, in the nursery, the infant's progress and weight were closely observed for at least ten days.

The response of the infant at birth has been constantly quoted in the results. For practical purposes four groups have been defined; the first consisted of infants which responded normally, that is their breathing, colour and vitality were satisfactory within four minutes of birth. Those infants which required five to ten minutes to attain normal standards were said to respond abnormally slowly. When resuscitation took ten to twenty minutes the response was considered to be very slow and shock was certainly present. The last, or fourth group of infants, included those whose condition was abnormal after twenty minutes. It was probable that such cases were not only suffering from severe shock but also from cerebral damage or pulmonary complications.

Specimens of blood for biochemical examination were obtained from the foetal circulation by cutting the umbilical cord and allowing the blood to run from the end attached to the placenta into a test tube. The blood was never taken until the cord had ceased to pulsate, but always within five minutes from the birth of the child. The maternal blood was then procured by venepuncture without delay, except in complicated deliveries when there was sometimes an

interval of half an hour, owing to the inability to perform the venepuncture. When the babies were stillborn the blood had to be aspirated from the heart. The amount of clotted blood required was 7 to 10 c.c. and uncoagulated was 3 to 4 c.c. From these samples sugar was estimated by using 0·2 c.c. non-coagulated blood for the micro-modification of the Folin Wu technique. For the non-protein nitrogen and the serum protein determinations, the micro-Kjeldahl method was adopted and for the analysis 3 c.c. serum were used. The chlorides were estimated by the standard Van Slyke process, and the sodium colorimetrically.

Results

There were twenty-eight blood-sugar estimations upon the mother and forty-four upon the newborn infant. The results are shown on table 1 where it is revealed that the blood-sugar in the mother was invariably higher than in her infant except in one instance when a craniotomy had been performed. There was, however, a wide range of normal as demonstrated by the following summary:—

	NO. OF CASES	BLOOD SUGAR MGM. PER CENT.	AVERAGE BLOOD SUGAR MGM. PER CENT.
Mother	28	90–229	140
Infant: over 5½ lb.	25	79–190	125·4
3 to 5½ lb.	10	82–166	121·6
Under 3 lb.	5	38–69	52
Stillbirths: over 5½ lb.	2	49–82	65
Craniotomy	1	—	48
Craniotomy	1	—	400

The marked variation in the mother was dependent upon numerous factors; toxaemia of pregnancy, antepartum haemorrhage, excitement on the part of the mother during labour, prolonged labour and instrumental deliveries. These all tend not only to raise the mother's blood-sugar but also the infant's, either directly or indirectly. The influence of carbohydrate intake and anaesthesia could not be demonstrated. The relationship between the clinical condition of the baby and its blood chemistry is revealed by the fact that ten out of twenty-one infants, i.e. almost 50 per cent., with a blood-sugar of 110 mgm. per cent., or more were shocked at birth, whereas out of those with a lower blood-sugar only one in fourteen, i.e. 7 per cent., was shocked. It is interesting to see that although distressing signs have been noted in both mother and infant, most infants live and progress normally. Even the initial physiological loss of weight in infants with a high and a low blood-sugar is on the average approximately 7 oz. in each group.

The non-protein nitrogen of the blood depends upon the urea, amino-acid, creatinine, uric acid and residual nitrogen content in the blood; therefore, it is not surprising that its value varies considerably in mother and infant at the time of parturition (see table 2). In the forty mothers examined it ranged from 28 to 60 mgm. per cent. and the average was 37 mgm. In contrast to this the maximum and minimum values in forty-one infants were 24 and 64 mgm. respectively and their average was 40 mgm. The majority of the infants

87·5 per cent., had higher values than their mothers, but this figure may be slightly inaccurate as the mothers who underwent caesarian section were the ones to have higher non-protein nitrogen than their babies, and it was also in these mothers that there was a delay in obtaining samples of blood. The prognostic significance may be summed up by stating that three out of seventeen infants, i.e. 18 per cent., with a non-protein nitrogen of less than 40 mgm. per cent. were shocked, while almost half the infants with a higher value exhibited shock. Nevertheless, the patients even with the maximum value of 64 mgm. generally made an uninterrupted recovery.

The serum protein, albumin and globulin in twenty-two mothers and their infants have been correlated with the clinical state of the infant at birth (see table 2). A summary of the figures is as follows :—

	MOTHER, GRAMMES PER CENT.	INFANT, GRAMMES PER CENT.
Serum albumin : range	3·18–4·12	3·24–3·95
Average	3·72	3·67
Serum globulin: range	1·25–2·50	1·38–2·38
Average	2·05	1·99
Serum protein: average	5·77	5·66

They are lower than in normal adults and this reduction is more marked in the albumin fraction than in the globulin fraction. The reduction is not only absolute but also relatively greater in the infant than in the mother. It should not be assumed from these figures that the maternal values are invariably higher than the infant's, since 44 per cent. of the infants had a higher albumin blood content than their respective mothers. The results of the serum albumin and total protein bore no relationship to the clinical picture of the infant, or to its weight progress. The globulin fraction, however, was of prognostic value. If it fell below 2·06 grammes per cent. in the mother or 2·0 in the infant there was foetal distress or subnormal vitality in nine out of eleven infants, i.e. 78 per cent., at birth. On the other hand only three out of eleven infants (27 per cent.), with a higher globulin exhibited subnormal activity at birth.

Little need be said about the serum sodium and plasma chlorides of the blood detailed in table 3, as the latter does not influence the infant's general condition at birth, nor does it modify the infant's weight progress. The former, however, illustrates how a low serum sodium of 326 mgm. or less is associated with unmistakable signs of shock in 43·5 per cent. of such cases, i.e. seven out of sixteen cases. On the other hand, out of the fourteen infants with a higher value for the blood sodium only one (7 per cent.) was suffering from a similar degree of shock. A summary of the findings is given below:—

	MOTHER		INFANT	
	CASES	MGM. PER CENT.	CASES	MGM. PER CENT.
Serum sodium: Range	29	306–345	29	308–350
Average		322		326
Plasma chloride: Range	22	421–538	23	351–468
Average		465		432

These figures show how both these constituents of the blood are sometimes below the normal adult level. The sodium values are not predominantly

TABLE 1

CASE	MOTHER		LABOUR HOURS	DELIVERY	BIRTH WEIGHT LB. OZ.	INITIAL WEIGHT-LOSS OZ.	REMARKS AND INFANT'S CONDITION	SUGAR MGM. PER CENT.	
	AGE	PARA						MOTHER	BABY
24B	42	3	24½	Spontaneous	6 3	1	Very shocked indeed. Mother severe pre-eclamptic.	—	190
35	40	0	7¾	Spontaneous	7 6½	10	Responded well. Mother exhausted and thirsty. Had no solids or fluid.	172	168
23B	41	2	0	Caesarian	4 3	11	Responded well. Mother severe A.P. haemorrhage and was severely shocked during operation.	229	160
21	21	0	0	Caesarian	7 3	—	Responded poorly. Lived few hours. Appeared cerebral. Mother severe pre-eclamptic.	—	166
30B	30	4	5	Spontaneous	4 5	—	Very shocked indeed. Lived only a few hours. Mother eclamptic.	—	162
13	24	2	6¾	Spontaneous	7 8	10½	Shocked. Mother eclamptic.	200	160
2	21	2	19	Caesarian	8 15	1¼	Foetal distress. Responded very slowly indeed.	267	160
20B	36	0	11½	Forceps	4 12	—	Very shocked. Died in 5 hr. due to A.P. haemorrhage and Willett's forceps.	—	154
3	20	0	21½	Spontaneous	5 11½	8	Responded well. Mother mild pre-eclamptic.	150	148
1	25	0	26½	Spontaneous	6 3½	4½	Shocked. Labour prolonged by disproportion.	160	145
16	30	0	33	Forceps	6 15	10½	Shocked. Mother pre-eclamptic.	145	133
26	32	0	17½	Forceps	5 14	9½	Very shocked indeed. Had foetal distress.	—	133
34	22	0	9½	Spontaneous	8 2	11	Responded well. Took fluids freely during labour.	133	133
4	19	0	21	Breech	6 2	3½	Responded well. Mother severe pre-eclamptic.	132	129
38	34	0	7	Forceps	7 0	10½	Responded slowly. Prolonged difficult labour. Silent first stage.	131	128
5	22	0	29	Spontaneous	8 6	9½	Responded well. Prolonged labour due to twilight sleep.	127	127
7	28	0	37¾	Breech	6 8	4	Responded very slowly—very shocked.	145	123
32	27	0	10½	Spontaneous	6 12	9	Responded well. Had shown foetal distress. Large caput. Mother took glucose drinks.	131	121
17	21	0	0	Caesarian	3 6½	6	Very shocked. Mother severe pre-eclamptic.	160	114
6	24	0	9	Forceps	5 11½	0	Responded fairly well. Had foetal distress.	128	114
8	20	0	19½	Forceps	8 0½	5	Very shocked. Difficult labour.	114	110
29B	36	0	15	Spontaneous	3 8	2	Responded well. Twin to 29A.. Mother mildly toxic	—	109
18	40	4	0	Caesarian	7 9¾	3¾	Responded well. Mother had cardiac damage.	114	107
11	24	0	23	Breech	6 0	0	Responded well. Prolonged labour due to inertia.	110	107

10B	31	0	19¾	Breech	5	15	11	Responded fairly well. Binovular twin to 10A. Mother mild pre-eclamptic.	118	106
19	30	0	16	Spontaneous	7	2¾	8	Responded slowly. Mother severe pre-eclamptic.	128	106
39	36	0	20	Caesarian	5	6¼	0	Very shocked indeed. Operation to save infant.	100	98
29A	36	0	14½	Breech	3	0	1	Responded well. Uniovular twin to 29B. Mother mildly toxic.	—	98
37	28	1	2	Caesarian	6	8¾	6	Responded well. Operation for flat pelvis. No fluids taken.	94	94
41	31	2	2	Caesarian	6	10	0	Responded well. Mother had cardiac damage.	97	91
40	19	0	1¾	Spontaneous	6	13½	6½	Responded well. Mother fairly severe pre-eclamptic.	90	90
36B	41	6	3½	Breech	7	9½	12	Responded well. Binovular twin to 36A.	115	88
10A	31	0	18¾	Spontaneous	3	13½	3	Responded well. Binovular twin to 10B. Mother mild pre-eclamptic.	118	82
43	25	1	11¾	Spontaneous	5	1	—	Responded well. Mother slightly toxic.	103	82
36A	41	6	3	Breech	8	0½	12	Responded well. Binovular twin to 36B. No fluid taken by mother.	115	79
20A	36	3	7	Spontaneous	1	4	—	Died within ½ hr. of birth.	—	69
19	20	0	0	Caesarian		10	—	Died within ½ hr. of birth. Mother severe pre-eclamptic.	—	67
9	33	0	0	Caesarian	2	14	—	Died within ½ hr. of birth. Mother severe pre-eclamptic.	—	47
46	35	3	10	Breech	2	4	—	Died within 6 hr. of birth. Mother had pelvic peritonitis.	—	40
42	21	0	0	Caesarian	1	5	—	Died within ½ hr. of birth. Mother severe pre-eclamptic.	—	38
28	20	0	14½	Craniotomy	6	+	—	Still birth. Head perforated when infant was dead, as hydrocephalic.	—	48
32	31	0	48	Forceps	7	3	—	Still birth. Foetal heart had failed 10 hr.	—	49
20C	23	0	31	Spontaneous	7	8	—	Still birth. Foetal heart had failed ½ hr. Adrenaline injected into heart.	—	82
45	27	0	42½	Craniotomy	6	+	—	Still birth. Head perforated as hydrocephalic.	—	400

TABLE 2

CASE	MOTHER		LABOUR HOURS	DELIVERY	BIRTH WEIGHT LB. OZ.	INITIAL WEIGHT-LOSS OZ.	REMARKS AND INFANT'S CONDITION	ALBUMIN GRAMMES PER CENT.		GLOBULIN GRAMMES PER CENT.		PROTEIN GRAMMES PER CENT.		N.P.N. MGM. PER CENT.	
	AGE	PARA						MOTHER	BABY	MOTHER	BABY	MOTHER	BABY	MOTHER	BABY
15	30	0	18¾	Spontaneous	8 8½	6½	Responded well.	3·80	3·94	2·31	2·38	6·11	6·32	30	30
20	27	1	0	Caesarian	7 13	12	Responded fairly well. ? Due to morphine.	3·76	3·37	2·31	1·92	6·07	5·29	28	24
23A	22	2	24	Spontaneous	6 12½	6	Responded well.	3·19	3·31	2·50	2·25	5·69	5·56	32	30
12	24	0	15½	Spontaneous	7 10	6	Responded well. Had large caput.	4·05	3·95	2·10	2·30	6·15	6·25	32	32
22	31	0	30½	Forceps	8 4	14½	Foetal distress. Responded well.	3·18	3·24	1·63	1·56	4·81	4·80	31	32
18	40	4	0	Caesarian	7 9¾	—	Responded well. Mother cardiac case.	3·76	3·82	1·99	1·92	5·75	5·74	38	34
30B	30	4	5	Spontaneous	4 5	—	Very shocked. Died first day. Eclampsia.	3·70	3·41	1·85	1·95	5·55	5·36	32	35
31	29	0	15	Spontaneous	1 11	—	Died at birth. Anencephalic.	3·76	3·26	1·92	1·71	5·68	4·97	39	34
6	24	0	9	Forceps	5 11¾	0	Foetal distress. Responded fairly well.	—	—	—	—	—	—	—	35
7	28	0	37¾	Breech	6 8	4	Very shocked. Difficult delivery.	—	—	—	—	—	—	33	35
11	24	0	33	Breech	6 0	—	Responded well.	—	—	—	—	—	—	36	37
27A	22	0	34¾	Spontaneous	7 5	6	Responded slowly. Due to twilight sleep.	3·99	3·90	2·33	2·18	6·42	6·08	35	38
31A	20	0	54	Caesarian	7 3¾	4	Responded slowly. +Foetal distress.	3·82	3·63	2·04	2·22	5·86	5·85	35	38
17	21	0	0	Caesarian	3 6½	6	Very shocked. Mother severe pre-eclamptic.	3·89	3·71	2·14	2·24	6·03	5·95	—	—
3	20	0	21½	Spontaneous	5 11½	8	Responded well. Mild pre-eclampsia.	—	—	—	—	—	—	33	39
41	31	2	2	Caesarian	6 10	0	Responded well. Local anaesthesia.	—	—	—	—	—	—	34	39
38	34	0	7	Forceps	7 0	10½	Responded slowly. Difficult delivery.	—	—	—	—	—	—	34	39

29B	30	0	14½	Spontaneous	3	8	—	Responded well. Twin to 29A.	4·12	3·87	2·25	2·00	6·37	5·87	36	39
25	30	0	12	Forceps	8	4	—	Very shocked. Mother pre-eclamptic.	3·90	3·75	2·13	1·38	6·03	5·13	36	40
27B	27	0	16¼	Forceps	8	0	—	Very shocked. Developed haemorrhages.	3·81	3·78	2·0	1·78	5·81	5·56	38	40
24A	23	0	12¼	Spontaneous	7	11½	6	Responded well. Had large caput.	3·92	3·82	2·06	2·00	5·98	5·82	39	40
8	20	0	19½	Forceps	8	0½	5	Very shocked. Difficult delivery.	—	—	—	—	—	—	39	—
23B	41	2	0	Caesarian	4	3	1½	Responded fairly well. Due to A.P.H.	—	3·66	—	2·01	—	5·67	—	40
14	27	0	93½	Forceps	7	8	—	Very shocked indeed.	4·11	3·74	2·13	2·25	6·24	5·99	42	40
13	24	2	6¾	Spontaneous	7	8	10½	Shocked. Mother eclamptic.	—	—	—	—	—	—	45	40
1	25	0	26½	Spontaneous	6	3½	4½	Shocked. + Foetal distress.	—	—	—	—	—	—	30	41
37	28	1	2	Caesarian	6	8¾	6	Responded well. Mother flat pelvis.	—	—	—	—	—	—	35	41
5	22	0	29	Spontaneous	8	6	9½	Foetal distress. Response fair.	—	—	—	—	—	—	36	41
40	19	0	1¾	Spontaneous	6	13½	6½	Responded well. Mother pre-eclamptic.	—	—	—	—	—	—	36	41
35	40	0	7¾	Spontaneous	7	6½	10	Responded well.	—	—	—	—	—	—	34	42
29A	30	0	14½	Breech	3	0	6	Responded well. Twin to 29B.	4·12	3·74	2·25	1·88	6·37	5·62	36	42
39	36	0	30	Caesarian	5	6¼	0	Very shocked indeed.	—	—	—	—	—	—	36	42
36A	41	6	3	Breech	8	0½	0	Responded well. Twin to 36B.	—	—	—	—	—	—	38	42
34	22	0	9½	Spontaneous	8	2	11	Responded well.	—	—	—	—	—	—	36	44
4	19	0	21	Breech	6	2	3½	Responded well. Mother pre-eclamptic.	—	—	—	—	—	—	36	44
26	32	0	17½	Forceps	5	14	9½	Very shocked indeed.	3·82	3·70	2·01	1·85	5·83	5·55	36	44
36B	41	6	3½	Breech	7	9½	—	Responded well. Twin to 36A.	—	—	—	—	—	—	38	44
30A	20	0	0	Caesarian	6	12½	6	Responded slowly. Pre-eclamptic.	3·72	3·67	1·86	1·88	5·58	5·55	40	44
28A	20	0	14½	Forceps		—	—	Died. Head perforated as hydrocephalic.	3·85	3·82	2·14	2·15	5·99	5·97	40	46
28B	28	0	34	Breech	8	10	6	Responded well. Had foetal distress.	3·79	3·8	1·96	2·02	5·75	5·82	43	46
32	27	0	10½	Spontaneous	6	12	9	Foetal distress. Responded well. Had large caput.	—	—	—	—	—	—	41	47
2	21	2	19	Caesarian	8	15¼	1¼	Responded very slowly.	—	—	—	—	—	—	61	49
24B	42	3	12½	Spontaneous	6	3	1	Very shocked indeed. Mother pre-eclamptic.	3·88	3·48	1·25	1·88	5·13	5·36	60	64

TABLE 3

CASE	MOTHER		LABOUR HOURS	DELIVERY	BIRTH WEIGHT LB. OZ.	INITIAL WEIGHT-LOSS OZ.	REMARKS AND INFANT'S CONDITION	MOTHER		BABY	
	AGE	PARA						SODIUM MGM. PER CENT.	CHLORIDE MGM. PER CENT.	SODIUM MGM. PER CENT.	CHLORIDE MGM. PER CENT.
4	19	0	21	Breech	6 2	3½	Responded well. Mother severe pre-eclamptic.	306	421	308	389
7	28	0	37¾	Breech	6 8	4	Very shocked. Inertia during labour.	313	445	310	398
8	20	0	19½	Forceps	8 0½	5	Very shocked. Difficult delivery.	314	538	310	445
10B	31	0	19¾	Breech	5 15	11	Very shocked. Twin to 10A. Born last. Mother pre-eclamptic.	325	445	314	433
15	30	0	18¾	Spontaneous	8 8½	6½	Responded well.	310	—	314	—
36B	41	6	3½	Breech	7 9½	—	Responded well. Twin to 36A. Born last. Binovular twin.	314	491	314	439
41	31	2	2	Caesarian	6 10	0	Responded well. Mother had gross cardiac damage.	314	445	314	421
9	33	0	0	Caesarian	2 14	—	Died in 1 hr. Mother severe pre-eclamptic.	320	480	316	456
36A	41	6	3	Breech	8 0½	0	Responded well. Twin to 36B. Born first. Binovular twin.	314	491	318	445
37	28	1	2	Caesarian	6 8¾	6	Responded well. Operation for flat pelvis.	326	445	318	427
6	24	0	9	Forceps	5 11¾	0	Foetal distress. Responded fairly well.	322	468	320	456
10A	31	0	18¾	Spontaneous	3 13½	3	Responded well. Mother pre-eclamptic. Binovular twin. Born before 10B.	325	445	321	445
2	21	2	19	Caesarian	8 15¼	1¼	Foetal distress. Responded badly. Operation for inertia and disproportion.	316	448	322	468
1	25	0	26½	Spontaneous	6 3½	4½	Foetal distress. Shocked due to disproportion.	319	456	324	445
11	26	0	33	Breech	6 0	0	Responded well. Primary inertia.	311	451	325	451
14	27	0	93½	Forceps	7 8	—	Very shocked indeed. Large caput. Became cerebral.	322	—	326	—
23	22	2	24	Spontaneous	6 12½	6	Responded well. Easy labour.	323	—	327	—
40	19	0	1¾	Spontaneous	6 13½	6½	Responded well. Mother severe pre-eclamptic.	327	480	327	468
38	34	0	7	Forceps	7 0	10½	Foetal distress. Responded slowly. Very difficult labour.	332	462	329	445
20	27	1	0	Caesarian	7 13	12	Responded fairly well. Due to morphine and hyoscine. Mother flat pelvis.	335	—	333	—
34	22	0	9½	Spontaneous	8 2	11	Responded well.	318	503	333	445
22	31	0	30½	Forceps	8 4	14½	Foetal distress. Responded well. Mother severe pre-eclamptic.	330	—	334	—
12	24	0	15½	Spontaneous	7 10	6	Responded well. Had large caput.	335	—	338	—
5	22	0	39	Spontaneous	8 6	9½	Foetal distress. Responded fairly well. Twilight sleep responsible.	315	480	339	445
3	20	0	21½	Spontaneous	5 11½	8	Responded well. Mother mild pre-eclamptic.	333	433	340	433
39	36	0	20	Caesarian	5 6¼	0	Very shocked indeed. Operation to save child.	324	—	341	—
32	27	0	10½	Spontaneous	6 12	9	Foetal distress but responded well. Large caput.	323	433	345	433
13	24	2	6¾	Spontaneous	7 8	10½	Responded slowly. Mother eclamptic.	345	527	350	453
35	40	0	7¾	Spontaneous	7 6½	10	Responded well.	344	445	350	386

higher in the mother or the infant, in contrast to the chloride values, which were always higher in the mother with one exception in a case of caesarian section.

Discussion

The behaviour of the blood chemistry at birth will now be discussed under the headings of the various constituents which have been investigated. The results will be compared with those of other authors and an attempt will be made to state the factors responsible for the unexpected findings. Firstly, the blood-sugar levels have been shown in the past to be unusually high as compared with the fasting level in the normal adult. In the present series, values have been obtained which are on the average approximately 20 mgm. higher in both mother and infant than those recorded by previous authors.

	SUGAR (MGM. PER CENT.)	
	MOTHER	BABY
Howe and Given (1923)	125·0	103·0
Sherman (1925)	—	115·4
Ketteringham and Austin (1938) ..	124·0	103·6
Present series	140·0	125·4

The higher level can only be accounted for by the introduction of results obtained from mothers suffering from toxaemia of pregnancy, ante-partum haemorrhage, unduly long labour and abnormal deliveries. This high figure is only temporary for Ketteringham and Austin (1938) state that the normal adult fasting level appears in infants three to six hours after birth. Factors known to be responsible for this phenomena are anaesthesia (Ketteringham and Austin, 1938) and those already mentioned, and they achieve this physiological process by liberating an abundant supply of adrenaline into the circulation. In addition hyperglycaemia may result from a diminished production of insulin kinase secondary to portal stasis or hepatic insufficiency, for Thompson and Wilkinson (1940) have shown that children suffering from severe burns or scalds may develop an abnormal laevulose tolerance test.

Hypoglycaemia in the newborn has seldom been recorded, and the present investigations show that infants with a blood-sugar of under 70 mgm. per cent. at birth do not live more than four hours. A suspected case reported by Ehrich (1934) was thought to be due to diabetes in the mother, but it is now shown that this is not the only cause. Prematurity probably plays an important part; five infants weighing less than 3 lb. all had hypoglycaemia and died soon after birth. Further evidence is given by Van Creveld (1929) who found hypoglycaemia frequently in premature infants during the first month of life. The fact that it is confined to the premature infant is an argument for the functional immaturity of the liver. Even in the mature infant the glycogen storage of the liver and the placenta may be relatively less than that in the mother, as her blood-sugar is invariably higher.

The present biochemical investigations reveal that the non-protein nitrogen is also exceptionally high in mother and infant, their average being 37 and 40 mgm. per cent. respectively. The values for infants approximate to those

quoted by Lucas et al. (1921) and Bruch and McCune (1936). Their figures were 35 and 42 mgm., but the retention of the waste products of metabolism definitely decreases on the third day of life when the average values are 32 to 36 mgm. per cent. (Lucas et al., 1921; Bruch and McCune, 1936). Why this should happen and why the maternal values are not constantly lower than the infant's is unknown. If it were due to shock, the non-protein nitrogen would tend to be higher with increased trauma as is observed in the present cases. If trauma is a controlling factor either the mother or the infant can be subjected to the greater strain and therefore either person can have the maximum non-protein nitrogen. An additional factor modifying the results, might be a temporary renal impairment in the mother at parturition, as indicated by her raised urea nitrogen which is relatively greater than in the foetus (Howe and Given, 1923). Another possible explanation may be that the placental function alters during labour, causing an impairment in the excretion of the waste products of metabolism.

The serum proteins in the newborn are particularly low, as has been shown by previous investigators.

	CASES	ALBUMIN GRAMMES PER CENT.	GLOBULIN GRAMMES PER CENT.	TOTAL PROTEIN GRAMMES PER CENT.
DARROW AND CARY (1933)				
Mature infants	20	3·73	1·78	5·52
Premature infants	26	3·58	1·18	4·94
PRESENT SERIES	22	3·67	1·99	5·66

The total protein does not long remain low, for each day it rises until it is 6·23 grammes per cent. on the third day of life (Marples et al., 1932). Thereafter it rises gradually to attain adult levels by the eighteenth month of life (Rennie, 1935). The rapid initial rise in the amount of protein needs explaining. The subnormal values probably depend upon the state of development of the liver, which would account for the low values characteristic of the premature infant. The rapid rise of the serum proteins during the first three days of life may be due solely to the concentration of the blood, possibly precipitated by shock. Or it may be a physiological process to compensate for an exceptionally large blood-volume prior to birth. The latter possibility is supported by the observation of Oberst and Plass (1936) that the large blood-volume in the pregnant woman returns to normal or even subnormal at parturition; the foetal circulation may be similarly affected.

The sodium estimations gave results identical with those of the only similar investigation found in the English literature (Bruch and McCune, 1936). Bruch showed that the sodium rose from 325·7 mgm. per cent. at birth to 332·5 mgm. on the second day of life and thereafter altered only slightly. The low values in the mother and the infant compared with those in the normal adult may be interpreted as evidence either of shock or of adrenal insufficiency. The former suggestion is supported by the observation that marked shock is six times more frequent in infants with a serum sodium below 327 mgm. per cent. than in those with a serum sodium either equal to or greater than this amount. The only evidence of adrenal insufficiency is given by Miller (1941)

who noted that the administration of desoxycorticosterone reduced the initial physiological loss of weight at birth. Archidmede (1940) obtained similar results by means of this hormone but in premature infants. The chloride of the blood in both mother and infant is also surprisingly low in some instances. This cannot be due to blood dilution or to alteration in the alkali reserve (Matter, 1931), so that no valid reason can be given to explain it.

Conclusion

The blood chemistry of both mother and infant is disturbed at the time of birth, and haemoconcentration occurs in the infant during the first three to forty-eight hours of life. The biochemical changes may be summarized as follows: There is normally a transient rise in the blood-sugar which is constantly greater in the mother; the non-protein nitrogen is also elevated in both mother and infant but the rise is more marked in the latter; the serum proteins and albumin are always below the average adult level, whereas the globulin factor occasionally attains the average normal figure for man. The diversion from normal is usually more pronounced in the infant than in the mother. Lastly, the sodium content and chloride content of the blood, though frequently within normal limits, are sometimes exceptionally low. This affects more noticeably the estimations of sodium in the mother and of chlorides in the infant.

In the discussion an attempt was made to explain these findings on a physiological basis. In the mother the only rational explanation appears to be shock, occurring with or without its clinical manifestations. The baby's blood chemistry is obviously influenced by the biochemical constituents of the mother's blood, but the sudden alteration in the infant's mode of living and the need for it to adapt itself to its new surroundings introduce modifying factors. It was also observed that it was far commoner to find infants shocked when the blood chemistry was grossly deranged than when it was normal. The question then arises as to why the blood changes in the infant which are compatible with shock are not always associated with the clinical signs of the condition. At present this is unanswered, but it is suggested that if in a normal delivery the constituents of the infant's blood are suggestive of shock the clinical picture of this condition will only develop should trauma to the infant during labour become excessive. It was also interesting to note that these marked disturbances can be present for two or three days without producing deleterious effects upon the infant.

From the investigations upon the blood-sugar, non-protein nitrogen, serum globulin and sodium the following conclusions can be drawn. Firstly, it can be said that it is better for an infant to have a blood-sugar less than 110 mgm. per cent. at birth, for in such circumstances its vitality rarely gives cause for anxiety. If hypoglycaemia should be present the prognosis is bad; the infant, if premature, was found to weigh less than 3 lb. and generally died within an hour of being born, but if the infant was mature, it was stillborn. Secondly, the non-protein nitrogen concentration in the infant's blood varied with the clinical condition, shock being present in 18 per cent. of infants with less than

40 mgm. of the constituent as compared with almost 50 per cent. in infants with a higher figure. Thirdly, the serum globulin was an even better guide to the infant's clinical condition at birth. If it fell below 2·06 grammes per cent. in the mother or 2·0 grammes in the infant there was foetal distress or subnormal vitality at birth in 78 per cent. of cases, but if the globulin was higher, only 27 per cent. were similarly affected. Lastly, if the blood sodium was less than 327 mgm. per cent. 43 per cent. of the infants suffered from a marked degree of shock, but if the values were higher a similar degree of shock appeared in only 7 per cent. of infants.

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THE SECRETION OF URINE BY PREMATURE INFANTS

BY

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Previous work on the secretion of urine by full-term newborn infants has shown that their kidneys function rather differently from those of adults (McCance and Young, 1941). Premature infants have now been investigated because it was thought that the differences in function might be even greater at the earlier stages of development. Several oedematous infants have been included in the investigations, since Hallum's (1941) work suggested that had this not been done the work would have been incomplete. This author found that in a large series of infants 13·4 per cent. of those with a maturity of less than thirty-six weeks at birth developed 'oedema of the newborn,' whereas only 1·2 per cent. of those born at or nearer full term showed any sign of it. In Hallum's series the oedema always appeared within two or three days of birth, usually in the lower limbs, face, hands and genitalia. It was transient as a rule and subsided in about a week, but less frequently it progressed to generalized anasarca. Oedema of the lungs and of the larynx was sometimes observed in the later stages. The etiology is obscure and the literature not helpful. Hallum made a partial study of the blood chemistry and found that oedematous infants usually had high blood ureas. The range was 36 to 140 mgm. per 100 c.c. and the average 67 mgm. per 100 c.c. as against the 'normal' limits of 21 to 39 mgm. per 100 c.c. (Strictly speaking no premature infant can be regarded as normal, but in this article the infants who did not have oedema have been so designated.) The urine was noted to be scanty and 86 per cent. of the specimens contained a trace of albumin. This last, however, was not considered pathological, as von Reuss (1913) had found that 96 per cent. of the infants examined by him had albuminuria during the first four days of life. Histological examination of the kidneys of oedematous infants revealed no abnormality.

Material and methods

Infants admitted to the Municipal Premature Infant's Ward, City of Birmingham, were the subjects of the investigation. Their ages ranged from

two to eighteen days and their maturity was estimated to be thirty to thirty-six weeks. Both oedematous and 'normal' infants were tested during the first week of life. Some babies were tested again when they were about a week older; several of these had had oedema when first examined and had lost it during the interval.

Plasma protein was estimated by the micro-Kjeldahl method (Peters and Van Slyke, 1932). The collection of blood and urine and all chemical determinations other than that of plasma protein were made in the way described by McCance and Young (1941). There have been, however, a few female subjects in this investigation, and they voided their urine into small enamel bowls instead of hard glass test tubes. This was found to be satisfactory as premature infants are almost immobile and are nursed entirely in their cots. The error in the timing of each specimen was never greater than five minutes.

Results

The serum chemistry. Table 1 shows the serum chemistry of nineteen premature infants aged two to seven days, of whom seven were oedematous

TABLE 1
SERUM CHEMISTRY OF PREMATURE INFANTS

SUBJECT	AGE IN DAYS	UREA MGM. PER 100 C.C.	Na MGM. PER 100 C.C.	Cl MGM. PER 100 C.C.	PROTEINS GM. PER 100 C.C.
GROUP I. 'NORMAL' INFANTS AGED 3–5 DAYS					
Aa	3	17·0	348	368	5·27
Ws	3	41·0	345	377	4·86
Bs	3	15·0	—	318	5·36
Hu	3	14·8	340	368	4·00
C	3	22·5	353	359	5·11
Bt	4	29·5	326	385	5·15
R	4	99·6	342	385	4·18
Dy	4	39·0	300	—	4·27
Sm	4	39·2	293	380	4·14
St	4	27·0	346	415	4·83
E	5	10·0	358	386	3·62
Bg	5	30·7	342	348	4·71
GROUP II. OEDEMATOUS INFANTS AGED 2–7 DAYS					
Hs	2	90·0	340	397	3·73
L	2	51·0	350	342	4·55
Bl	2	103·6	371	386	4·5
X	4	120·0	—	—	—
Y	4	132·0	—	—	4·58
M	4	56·5	—	390	5·04
We	7	30·2	408	347	4·85
GROUP III. 'NORMAL' INFANTS AGED 8–18 DAYS					
M	8	26·0	332	400	4·96
Bl	8	25·0	304	380	3·80
Da	9	9·0	354	371	5·02
Bt	11	15·2	308	398	4·30
R	11	20·6	304	381	4·36
Dy	13	16·2	356	394	3·99
St	18	15·0	332	386	4·70
L	18	16·0	300	370	4·24

(groups I and II); and of eight infants aged eight to eighteen days (group III). One of the last was only examined once, but the others were babies who had been tested during the first week and their previous results are recorded in groups I and II.

The blood urea of the 'normal' infants in group I varied from 10 to 99·6 mgm. per 100 c.c. and in five it was above 29 mgm. per 100 c.c. All the infants with oedema (group II) had high blood ureas except We, aged seven days, whose oedema was subsiding on the day of the tests. The blood ureas in group III ranged from 9 to 26 mgm. per 100 c.c., and these figures resemble those obtained in a series of full-term infants aged seven to fourteen days, who were shown to have an average blood urea of 16·4 mgm. per 100 c.c. (McCance and Young, 1941).

As in full-term infants, both the sodium and chloride in the serum varied much more widely from infant to infant than they usually do from adult to adult. The chlorides were sometimes high compared with adult standards, and the sodium in the serum of two oedematous infants (Bl and We) was above the normal adult range, and higher than that of any 'normal' infant.

The protein in the plasma of premature infants ranged from 3·62 to 5·27 gm. per 100 c.c. These figures are low by adult standards (6 to 8 gm. per 100 c.c.), but are not necessarily abnormal, for it has been shown that the plasma proteins tend to be low until the second year of life (Mello-Leitao, 1916; Hickmans, 1940). The plasma proteins of the oedematous infants, with a range of 3·73 to 5·04 gm. per 100 c.c., were not any lower than those of 'normal' infants, and in all who were re-examined the plasma proteins had fallen a little during the interval. In Hallum's preliminary investigation, however, some oedematous infants had very low plasma proteins (2·7 to 4·1 gm. per 100 c.c.), and in several they were higher after the oedema had subsided.

The urea clearances. Fig. 1 shows the urea clearances (UV/P), of all the premature infants plotted against their minute volumes. It will be noted that: (1) The minute volumes varied from 0·005 to 0·333 c.c. per minute. (2) The urea clearances ranged between 0·025 and 2·43 c.c. per minute. (3) The urea clearances varied with the minute volumes. (4) The minute volumes, and consequently the urea clearances, were frequently low in babies with oedema, but at comparable minute volumes the clearances of oedematous infants were really no lower than those of the 'normal' infants. It is probable, therefore, that the high blood ureas of the oedematous infants were solely due to the low minute volumes. This is supported by the fact that baby R, who had not got oedema but was passing comparably small volumes of urine, had a blood urea of 99 mgm. per 100 c.c. After the infants had lost their oedema their minute volumes, urea clearances and blood ureas were all found to be in the 'normal' range. All the clearances will therefore be considered together when comparisons are being made with full-term babies and with adults.

In premature as in full-term infants the magnitude of the urea clearances at any particular minute volume varied considerably from one child to another

and sometimes in the same child from day to day; nevertheless it was the rule for the clearances of each baby to increase steadily with the minute volume.

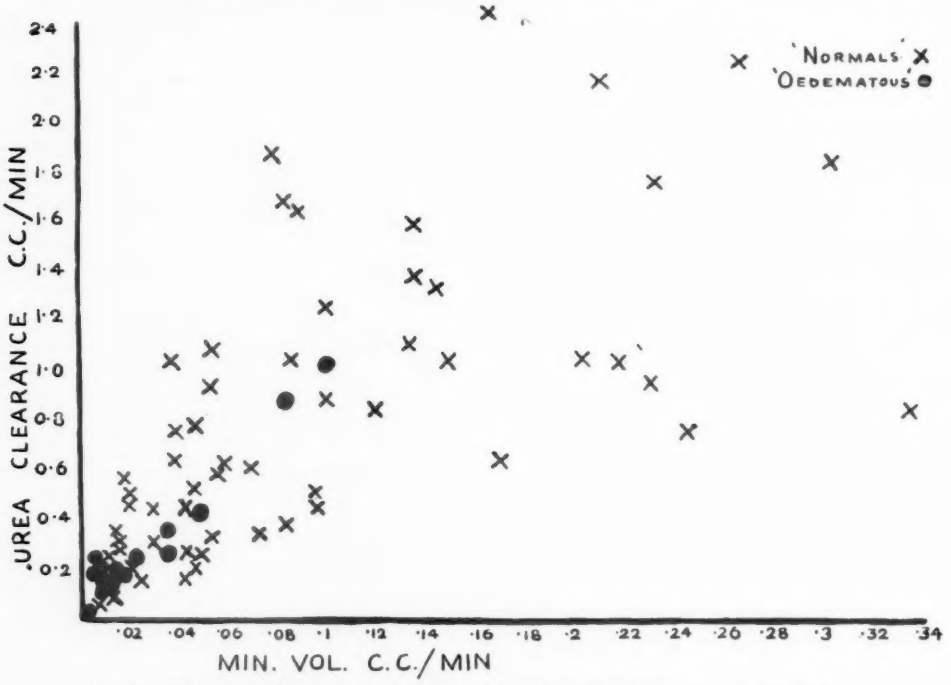

FIG. 1.—The urea clearances of ' normal ' and oedematous premature infants.

In order to compare the urea clearances of premature and full-term infants the individual minute volumes and clearances were corrected for surface area. At both ages the minute volumes were separated into four groups, and the clearances and minute volumes in each group were averaged. The results, which are given in fig. 2, show that at similar minute volumes the premature infant clearances were considerably lower than those of full-term infants. The urea clearances of the latter have already been shown to be very low compared with those of adults (McCance and Young, 1941).

In the investigation of full-term infants some inulin and urea clearances were estimated simultaneously. It was found that both varied together with the minute volume, and this has also been found to hold in infants with gastroenteritis. In all babies, therefore, it would seem that the variations in the urea clearances may be used as a guide to the behaviour of the glomerular filtration rates. If this be so the glomerular filtration rate (per metre surface area) is even lower in premature infants than it is in full-term infants and, as in them, it varies quite extensively with the minute volume. A similar association has been met with in adult rabbits at all minute volumes (Kaplan and Smith, 1935; Wilkinson and McCance, 1940), and in pump-lung-kidney preparations of the dog a change in the minute volume has also been shown to accompany the change in glomerular filtration rate brought about by a rise or fall in the arterial blood pressure (Shannon and Winton, 1940). All the evidence tends to show that in infancy the urea clearances, and

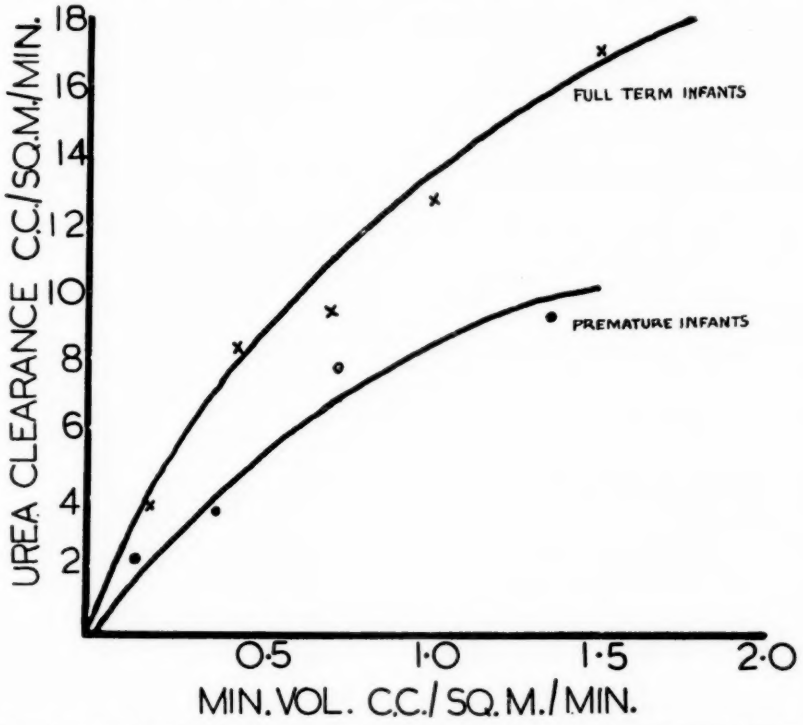

FIG. 2.—A comparison of the average urea clearances of full-term and premature infants.

hence the glomerular filtration rates, have not yet become as stable as they are in adult life.

A histological examination of the renal glomerulus in early postnatal life led Gruenwald and Popper (1940) to suggest that infants of this age might have low glomerular filtration rates. These authors observed that up to birth the glomerular loops were matted together and invaginated in a sac of high columnar epithelium. After birth the epithelial sac had burst and the loops expanded, but in early postnatal life the peaks of the loops were still covered with high columnar epithelium. Gruenwald and Popper considered that this layer might impede glomerular filtration.

The excretion of minerals. The electrolytes are threshold substances and their clearances depend upon the concentration in the serum and the reabsorptive activity of the tubules as well as upon the glomerular filtration rates and the minute volumes. The tubules are partly under the control of extrarenal factors, and the suprarenal cortex is especially concerned with sodium, chloride and potassium.

The sodium and chloride clearances, plotted against their minute volumes, are shown in fig. 3. For graphical convenience nine sodium or chloride clearances at minute volumes over 0·2 c.c. per minute and two exceptionally high chloride clearances above 0·02 c.c. per minute have been omitted. It will be seen that the sodium and chloride clearances tended to rise with an increase in the minute volume, but there was a wide scatter. In several infants, whose sodium clearances are plotted on the base line, the urine contained only traces

of sodium even at fairly high minute volumes. Since the concentrations of sodium and chloride in the serum varied so much from infant to infant, the clearances at comparable minute volumes might have been expected to vary with them but, as in full-term infants, individual idiosyncrasies outweighed any such effects. Some children, for example, whose serum concentration was relatively high, had very low clearances.

Fig. 3 shows that the oedematous infants tended to have low sodium and

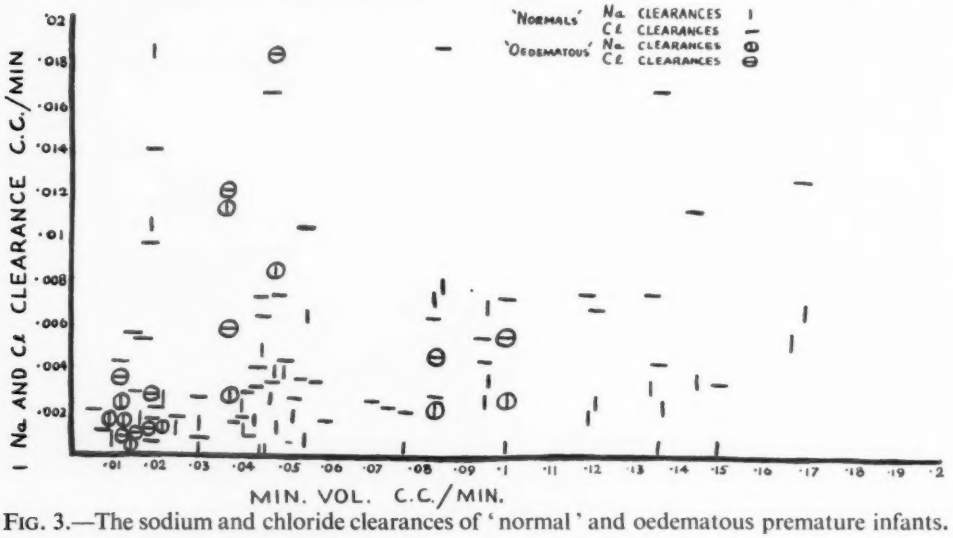

FIG. 3.—The sodium and chloride clearances of ' normal ' and oedematous premature infants.

chloride clearances at low minute volumes, but that at such minute volumes the clearances of ' normal ' infants were within the same range. All the clearances have therefore been included when the results were being averaged for comparison with those of full-term infants.

Few estimations of serum potassium were made, and potassium clearances could not therefore be calculated for premature infants. Since many were jaundiced at the time of the investigation, the serum level was probably high; the amount of potassium in the urine, however, was small, and the potassium clearances were probably quite as low as those of full-term infants.

The sodium, chloride and potassium clearances of full-term infants were found to be low compared with those of adults; a further comparison has now been made between the sodium and chloride clearances of full-term and premature infants. The concentrations of sodium and chloride in the sera were first averaged, and found to be the same in both groups. It was felt, therefore, that their clearances might safely be compared. Accordingly, both minute volumes and clearances were ' corrected ' for surface area and averaged as the urea clearances had been. The results are given in table 2. It is evident that not only the urea clearances, but also the sodium and chloride clearances were lower in premature than in full-term infants; moreover, the $\frac{\text{chloride}}{\text{urea}}$ and $\frac{\text{sodium}}{\text{urea}}$ clearance ratios show that the mineral clearances were relatively lower

than the urea clearances. If it is accepted that the urea clearances follow the glomerular filtration rates, the low $\frac{\text{mineral}}{\text{urea}}$ clearance ratios in premature infants are presumably due to a relatively higher rate of tubular reabsorption per c.c. of filtrate formed.

TABLE 2

A COMPARISON OF THE UREA, SODIUM AND CHLORIDE CLEARANCES OF FULL-TERM AND PREMATURE INFANTS

MINUTE VOLUME, C.C. PER SQ. M. PER MINUTE	FULL-TERM INFANTS					PREMATURE INFANTS				
	CLEARANCE, C.C. PER SQ. M. PER MINUTE			RATIO		CLEARANCE, C.C. PER SQ. M. PER MINUTE			RATIO	
	UREA	Na	Cl	$\frac{Na \times 100}{U}$	$\frac{Cl \times 100}{U}$	UREA	Na	Cl	$\frac{Na \times 100}{U}$	$\frac{Cl \times 100}{U}$
0·3	5·9	0·048	0·1	0·82	1·7	3·5	0·025	0·04	0·71	1·14
0·75	11·2	0·070	0·16	0·62	1·43	7·0	0·035	0·07	0·5	1·0
1·0	13·3	0·093	0·185	0·70	1·40	8·3	0·036	0·085	0·43	1·02
1·3	15·6	0·12	0·21	0·77	1·35	9·2	0·038	0·105	0·41	1·1

The osmotic pressure of the urine. It was found that the osmotic pressure, i.e. the concentration of solids, in the urine of full-term infants was low by adult standards, and that the ratio—

$$\frac{\text{m.eq. of electrolytes in the urine} + \text{m.eq. of urea (U)}}{\text{m.eq. of electrolytes in the plasma} + \text{m.eq. of urea (P)}}$$

never exceeded 1 and was usually below 0·5, even when the urine volumes were small. This relationship has been investigated in premature infants and, as at full term, the U/P ratios tended to be of a low order. Some, however, were over 1, and higher than any of those found at full term. This was unexpected, and led to a further analysis of the data. It then became clear that there was an undoubted association between the height of the U/P ratio and the concentration of urea in the blood. Baby R. showed this particularly well, for when he was first examined his blood urea was 99·6 mgm. per 100 c.c. and he had a U/P ratio of 1·1 with a minute volume of 0·34 c.c. per sq. m. per minute. On the second occasion his blood urea was 20·6 mgm. per 100 c.c., and when his minute volume was 0·32 c.c. per sq. m. per minute his U/P ratio was only 0·24. In table 3 the blood ureas and U/P ratios are set out over four limited ranges of minute volumes, and the general association of high U/P ratios with high blood ureas is clear. On re-examining the U/P ratios of the full-term infants, it was then found that the one child in that series who had had a high blood urea had also given a high U/P ratio. This child had a meningocoele and fever and, although the high ratio was mentioned, it was not discussed because it was felt that the child was not normal.

TABLE 3

THE RELATIONSHIP BETWEEN THE BLOOD UREA AND THE $\frac{U}{P}$ RATIO

SUBJECT	BLOOD UREA	$\frac{U}{P}$ RATIO	SUBJECT	BLOOD UREA	$\frac{U}{P}$ RATIO
(MIN. VOLS. 0·08–0·2 C.C. PER SQ. M. PER MINUTE)			(MIN. VOLS. 0·08–0·2 C.C. PER SQ. M. PER MINUTE)		
Bl	103·6	0·9	L	51	0·4
R	99·6	1·2	L	51	0·39
R	99·6	1·08	Bt	29·5	0·45
Hs	90	0·79	Bt	29·5	0·28
Hs	90	0·73	Bl	25·0	0·2
L	51	0·49	R	20·6	0·17
Sm	39·2	1·48	R	20·6	0·41
Sm	39·2	1·79	L	18·0	0·15
M	26·09	0·59	L	18·0	0·10
C	22·5	0·31	St	15·0	0·12
			Bt	15·2	0·20
(MIN. VOLS. 0·2–0·5 C.C. PER SQ. M. PER MINUTE)			Da	9·0	0·09
Bl	103·6	0·69	(MIN. VOLS. 1·0–2·16 C.C. PER SQ. M. PER MINUTE)		
R	99·6	1·1			
Hs	90·0	0·73	Bt	29·5	0·16
Ws	41·0	0·45	Bt	15·2	0·16
Sm	39·2	0·27	St	15·0	0·17
Bg	30·7	0·22	St	15·0	0·11
St	27·0	0·41	E	10·0	0·07
M	26·0	0·39	E	10·0	0·06
Bl	25·0	0·138	Da	9·0	0·09
R	20·6	0·24	Da	9·0	0·09
Bt	15·2	0·27			
E	10·0	0·078			

The connexion between high blood ureas and U/P ratios in infants is interesting from the point of view of their kidney function. The relationship would follow inevitably if the power to concentrate urea from blood to urine were unaffected by the height of the blood urea and the excretion of electrolytes. The reason is as follows: The osmotic pressure of both urine and blood can be regarded as due to electrolytes and urea, and the U/P written $\frac{Ue+Uu}{Pe+Pu}$. The plasma osmotic pressure is due mostly to electrolytes, and the urea is never an important part. The osmotic pressure of the urine may be due almost entirely to urea, and in babies, who have usually got very low electrolyte clearances, it generally is. Hence, doubling the urea in the blood may not sensibly alter the total osmotic pressure of this fluid, but doubling the urea in the urine may practically double its osmotic pressure, and the total U/P ratio. Returning to table 3 it will be seen that baby Sm in the low-minute volume group has exceptionally high U/P ratios with an almost normal blood urea. His high U/P ratios, and his failure to conform to the generalization which has just been made, were due to his electrolyte clearances which were very high, and far outside the usual range.

In adults the U/P ratios seldom exceeds 3. This is, so to speak, their

ceiling, and when that has been reached an increase in the fraction of the osmotic pressure ratio due to urea can only be achieved by a decrease in the fraction of the ratio due to electrolyte. It was at first thought that at low minute volumes the infants' kidneys were working at or about their limiting U/P ratios for total osmotic pressure. The observations now recorded suggest that this is not so, but that the concentration of urea and electrolytes are proceeding independently of each other, and that over the serum concentrations so far encountered in these studies neither are being limited by the total osmotic pressure of the urine.

Table 3 also shows what has been implied several times before, namely, that high blood ureas in infants only occur when the minute volumes have been low. In other words at this age a low urine output spells renal failure.

Causes of oedema

The susceptibility of premature infants to oedema is extremely interesting in the light of the present observations on their kidney function. It has been emphasized that no difference has been found between oedematous and 'normal' infants in this respect, except for the very small urine output of the former. When, however, the kidney function of premature, full-term infants, and adults was compared it was found that all infants, but particularly premature infants, had very low sodium and chloride clearances. More than that, evidence was obtained that premature infants probably reabsorbed more sodium and chloride per c.c. of glomerular filtrate than full-term infants, and these again than adults. A restricted output of salt goes naturally with a tendency towards water retention and consequently towards small urine volumes. This then is the reason why all premature babies are susceptible to oedema, but the low level of protein in the plasma may also be a contributory cause. The individual idiosyncrasies which determine the development of oedema may be very slight, and have so far escaped detection.

The causes of the low mineral clearances were discussed in the article on full-term infants. It was suggested that a low glomerular filtration rate, combined with an overactive suprarenal cortex might account for the findings. It was recognized, however, that the low potassium clearances could not be so explained. A better explanation now seems to be that the salt retention, water retention and oedema may be due to some over-action of the female sex hormones which can certainly produce these effects without, it seems, altering the potassium metabolism (Thorn and Emerson, 1940). The retention of sodium, chloride, and water in infancy is perhaps to be correlated with the well-known fact that at this age all infants contain more sodium and chloride per kgm. of body weight than adults (Shohl, 1939). The low mineral clearances may also be regarded as a protective mechanism, for the mineral intake of breast-fed infants is small while their rate of growth is rapid.

Summary

By determining the urea, sodium, chloride and sometimes potassium in the urine and in the capillary blood of premature infants it has been found that:

(1) As in full-term infants the urea clearances and probably the glomerular filtration rates vary extensively with the minute volume.

(2) Making surface area the basis of comparison, premature infants have lower urea clearances than full-term infants, but their sodium and chloride clearances are still more reduced, so that they have smaller $\frac{\text{sodium}}{\text{urea}}$ and $\frac{\text{chloride}}{\text{urea}}$ clearance ratios. It has been suggested that this underlies the tendency of premature infants to get oedema.

(3) The osmotic pressure of the urine of premature infants is generally very low and the U/P ratio is seldom over 1. The ratio may rise above 1 if the blood urea is high.

(4) Infants with oedema consistently excrete small volumes of urine, but their urea and mineral clearances are no lower than those of their 'normal' fellows at comparable minute volumes.

(5) Broadly speaking, the functional differences between adults and full-term infants are exaggerated in premature infants.

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FAMILIAL RENAL DWARFISM

BY

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A familial predisposition to arteriosclerosis with secondary malignant nephrosclerosis is well recognized, but that chronic interstitial nephritis may be a familial disease is more debatable, and in children even individual cases are rare. Mitchell (1930), in a comprehensive review of the literature of chronic interstitial nephritis in childhood (renal dwarfism), assessed the number of reported cases under twenty years of age as a little over two hundred, but in view of the recent increased interest in the disease, the number now might well be double this. He quotes eleven instances in which more than one child in the family was affected.

The following report deals with a family in which three and probably four of eight live-born children suffered from renal dwarfism. The first case, Mary B. was seen in 1933, when the diagnosis was established, but not again until she was dying of uraemia in 1938, when the other members of the family were investigated.

History of pregnancies. Both parents are healthy and now aged forty-four years. No history of kidney disease on either side of the family could be obtained. There have been nine pregnancies, the details of which are as follows:—

(1) John B., born in 1921, died when nine years old of meningococcal meningitis. The mother says he was healthy until the onset of the fatal illness.

(2) Daniel B., born 1922, is alive and well. This boy has not been examined or seen, but the mother reports him well (April, 1941).

(3) Joseph B., born in 1923, died at two years seven months of ' pneumonia.' This illness was associated with coma and rapid breathing, but there was no cough. He was ' always thirsty ' and Mrs. B. in the light of what she knows now advances the suggestion that he died of uraemia. (Probable case.)

(4) Mary B. (Case 1), born in 1924, was a renal dwarf and died in 1938. Her case is described in detail later.

(5) Violet B. (Case 2), born in 1928, was a renal dwarf, and died in 1939. Her case is described in detail later.

(6) Twins, born in 1931.

(*a*) Patsy B. (Case 3), a renal dwarf, is described in detail later.

(*b*) Bridget B., alive and well, was examined in April, 1938. At this time, height was 116·5 cm. (average 111 cm.); weight 21·8 kgm. (19·87 kgm.); urine normal; non-protein nitrogen 23·8 mgm. per cent. The mother reports her still well (April, 1941).

(7) Miscarriage, 1932.

(8) Bernadette B., born in 1934, is alive and well. When examined in April, 1938, aged three-and-a-half years, height was 93 cm. (average 92·7 cm.); weight 16·32 kgm. (15·0 kgm.); urine normal; non-protein nitrogen 20·6 mgm. per cent. She is still well (April, 1941).

(9) Miscarriage, 1936.

Detailed case reports

Case 1. Mary B., born September 22, 1924, came under observation on January 18, 1933, when eight years old because of polydipsia and polyuria (enuresis) of two years' duration. She was healthy at birth, breast fed for nine months, and throve and developed normally. She had measles at five years, whooping-cough at six years, and scarlet fever at seven years. The scarlet fever was not a severe attack and there were said to be no complications. When six years old (i.e. before the scarlet fever) the mother noticed that she was always drinking water and that she had begun to wet the bed at night. She was first seen at hospital on January 18, 1933, and was admitted for investigation.

PHYSICAL EXAMINATION. A small, spare child of average mentality; height 114 cm. (average 122 cm.); weight 19·8 kgm. (24·0 kgm.). The heart, lungs and abdomen did not show any evidence of disease; the ocular fundi were normal.

INVESTIGATIONS (January, 1933). The urine was pale, specific gravity 1002 to 1007; albumin, a trace on occasions only; no blood; no casts. The output in twenty-four hours varied from 74 to 122 oz. The urea concentration test showed 0·92 per cent. urea in the urine two hours after ingestion of 15 gm. urea. The phenosulphonephthalein test showed an excretion of only 11·2 per cent. following intramuscular injection of 6 mgm. of the dye. Non-protein nitrogen was 62·2 mgm. per cent. The blood pressure was systolic 124 mm. Hg and diastolic 92 mm. Hg. Tuberculin skin tests were negative. X-ray examination showed no rickets, but her bones were reported as small.

In April, 1933, she was readmitted and the following findings recorded. The urea concentration test gave 1·78 per cent. in second hour; phenosulphonephthalein test 8·7 per cent. in two hours; non-protein nitrogen 52·6 mgm. per cent.; chlorides 325 mgm. per cent.; total CO_2-combining power (alkaline reserve) 21·5 volumes per cent.; serum calcium 9·8 mgm. per cent.; serum phosphorus 6·9 mgm. per cent.; haemoglobin 70 per cent. (Sahli); erythrocytes 3,700,000 per c.mm.; leucocytes 17,300 per c.mm.

Considerable difficulty was experienced in getting the mother to co-operate and she would not allow the child to come to hospital again.

In January, 1938, she was seen by one of us at home in uraemic coma. As she was then too old for admission to the children's hospital (thirteen years three months), she was admitted to an infirmary where she died the next day (January 11, 1938). Permission for a post-mortem examination was not granted.

Case 2. Violet B. was admitted for observation on March 24, 1938, aged ten years. She had been healthy at birth, breast fed and throve well until six years of age (1936) when she had scarlet fever. Since then she had never been well and had become increasingly pale and listless. The mother had regarded her as merely lazy. No history of thirst, polyuria or enuresis.

PHYSICAL EXAMINATION. She was a small, spare girl with 'dried-up' appearance. Her complexion was sallow. Genu valgum was present and also slight enlargement of epiphyses at the wrist. Height 112 cm. (average 131·5 cm.); weight 22·56 kgm. (29·07 kgm). Examination of the heart, lungs and abdomen did not reveal any abnormality. Her ocular fundi were normal.

INVESTIGATIONS. The urine showed a low specific gravity (1002), a haze of albumin but no casts or blood cells. Blood pressure was systolic 120 mm. Hg, diastolic 75 mm. Hg. Urea clearance 14·8 per cent.; non-protein nitrogen 100 mgm. per cent.; serum calcium 9·4 mgm. per cent.; serum phosphorus 5·3 mgm. per cent.; phosphatase 16·8 units (Jenner-Kay method). X-ray examination of bones showed epiphyses wider than normal and changes typical of atrophic renal rickets.

In deference to the mother's wishes she was dismissed from hospital in two days. The mother was instructed to give her sodium bicarbonate 30 grains and calcium lactate 15 grains four times daily along with large doses of a vitamin A and D concentrate (45 drops daily), but it is doubtful if this was carried out. She died at home in Ireland on May 27, 1938, presumably in uraemic coma.

Case 3. Patsy B. was admitted for investigation on February 21, 1938. He was one of twins, healthy at birth and had been breast fed for one month, then on cow's milk. He was normal in size and development at one year, but had congestion of lungs at this time with good recovery. At two years it was noticed that the twin was growing much more quickly and the difference has become more marked in the intervening years. He has always been thirsty and has nocturnal enuresis.

PHYSICAL EXAMINATION. (Aged six years two months.) He was a small but well-covered boy, very dull mentally. Complexion was sallow and waxy. He had slight genu valgum. Height 92 cm. (average 112 cm.): weight 12·74 kgm. (20·48 kgm.). Nothing abnormal was found in heart, lungs or abdomen.

INVESTIGATIONS (February 21, 1938). The urine showed a specific gravity of 1008, a haze of albumin but no casts or blood. The blood pressure was systolic 92 mm. Hg, diastolic 40 mm. Hg. Urea clearance 37·7 per cent.; urea concentration test 0·80 per cent. in second hour after 15 gm. of urea; blood urea 82·6 mgm. per cent.; serum calcium 11·7 mgm. per cent.; serum phosphorus 5·0 mgm. per cent.; phosphatase 21·0 units (Jenner-Kay method). X-ray examination showed no evidence of rickets.

He was dismissed after three days in hospital on alkali, lactate and vitamin concentrate in the same doses as his sister Violet. He was readmitted for three days in June, 1939. Unfortunately the urea clearance figure was not obtained. The urea concentration test showed 0·59 per cent. in the second hour; non-protein nitrogen 79·3 mgm. per cent. The blood pressure was 104 mm. Hg systolic and 78 mm. Hg diastolic. His height had increased 6 cm. and his weight 1·4 kgm. in the intervening sixteen months. He is taking the alkali and vitamin concentrate irregularly, and the mother reported (April, 1941) that he was ' well ' but still small.

Remarks

All four cases of renal dwarfism occurred in successive pregnancies in the middle of the mother's child-bearing life. The significance of this is not clear. In the absence of post-mortem examination, no information is available about the underlying pathology. As is usual in such cases, hypertension was not present nor were casts found in the urine. Because of these features it has been suggested that renal dwarfism is more often due to congenital hypoplasia of the kidneys than to chronic nephritis. Coplin (1917) has suggested that the renal hypoplasia might be due to defective arteriogenesis with consequent defective development and scarcity of secretory units. Such an inherent fault in the germ plasm might explain the familial incidence. Congenital cystic disease of the

kidneys, an even rarer but recognized familial disease, might produce a similar picture but this is unlikely in the absence of palpable kidneys and hypertension.

Chemical poisons, particularly lead, causing chronic nephritis, were considered but with negative results. Infection also might have been responsible, especially infection of the urinary tract. In none of the three cases examined was there any sign suggestive of this. Nor was there any evidence that syphilis played any part although the Wassermann reactions were not done. The occurrence of the scarlet fever in the first two cases is probably a coincidence. The mother is quite emphatic that in the first case the thirst and polyuria preceded the scarlet fever, and that in the second case, the child's ill-health dated from this illness. The scarlet fever could then be a possible factor in only one of the cases and even in this one it does not seem likely that such a chronic lesion would develop so rapidly after the scarlet fever, although it should be noted that this patient did not give a history of thirst or polyuria, and, incidentally, was the only one who showed signs of renal rickets.

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CASE REPORTS

ARACHNODACTYLY IN A CHINESE INFANT

BY

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Marfan in 1896 described the first case of arachnodactyly occurring in a girl of five-and-a-half years of age. This patient had long and slender hands and feet, decrease in soft tissue, contractures of fingers, relaxed ligaments and other associated congenital abnormalities. He called the condition ' pieds d'arraignée,' because of the long, thin, spider-like feet. The term arachnodactyly (' spider digits ') first used by Achard in 1902 has been retained although it describes only one of the many abnormalities in these cases. Other synonymous terms are hyperchondroplasia (Méry and Babonneix, 1902), ' a case of atavism ' (Poynton, 1903), acromacrin (Pfaundler, 1914).

Pathogenesis

In 1920, Thursfield dealt briefly with the following two theories of causation of the disease: (1) That it is due to an endocrine disturbance, and (2) that it is in the nature of a primary muscular dystrophy. He thought that the balance of evidence was in favour of the latter theory, but later Ormond and Williams (1924) reviewed the above two theories in greater detail and were not inclined to favour either. They said that arachnodactyly is analogous to mongolism and not to cretinism, since there are usually associated with it several congenital malformations which are present in mongolism but not in cretinism, and as these congenital malformations have failed to react to endocrine therapy, they concluded that the condition could not be of endocrine origin. They have dismissed the second theory (that it is in the nature of a muscular dystrophy) as unsound because they found it difficult to correlate the characteristic symptom of muscular dystrophy, viz. the wasting, with the striking congenital abnormalities. Arachnodactyly is unassociated with a progressive course as occurs in typical muscular dystrophy. The developmental theory of this disorder, to which Ormond and Williams are inclined, is the most widely accepted theory at present. It is said to be due to a disturbance of mesoblastic growth, various mesodermal elements of the body structure having been affected in the early weeks of foetal life. With the exception of the eyes, only mesoblastic tissues are involved. Most probably the lens, which is of ectodermal origin, is secondarily affected by the weakening of the supporting tissues which most authors believe to be of mesodermal origin.

Clinical manifestations

Arachnodactyly or Marfan's syndrome is a congenital developmental anomaly characterized by an increase in the length of the long bones particularly distally. The abnormalities associated with arachnodactyly are not ordinarily detected until the second or third year of life. There are usually ' spider digits,' a slender skeletal development, a spur-like projection of the calcaneus which is especially characteristic, a long narrow thorax which is frequently funnel-shaped, and a high degree of asthenia. The joints and ligaments are abnormally weak, and grotesque displacements of the feet and ankles are possible. Occasionally contractures of ligaments, such as Dupuytren's contracture, occur. The face may have an appearance of maturity because of the decrease or absence of soft tissues; the bulbus oculi are deeply set because of the small amount of orbital fat. X-ray examination sometimes shows a premature development of the ossification centres and early disappearance of the epiphyseal lines.

There are also associated malformations and defects: those in the eyes (in about fifty per cent. of cases) include persistence of the pupillary membrane, tremulous iris, subluxation of the lens, nystagmus, myopia, colour-blindness. In the heart a patent foramen ovale has been reported. According to Piper and Irvine-Jones (1926) congenital defects of the heart form a classical combination. Club feet, flat feet and syndactyly have been reported. The associated structural defects are variable. They are deformities of the ear, webbing of the toes, kyphoscoliosis and thickening of the base of the skull. The intelligence is in most cases normal but may be defective.

Case report

A male Chinese Cantonese infant, aged seven months and fifteen days, was referred by the Lady Medical Officer in charge of the out-patient department, who stated that there was deformity of the skull with slight spasticity of the lower limbs, that on lifting the infant up with the hands under both axillae the limbs were crossed, that the knee-jerks were exaggerated and that the plantar reflex was an extensor response. A diagnosis of Little's disease had been considered.

History. The infant was born at full term by breech delivery on November 5, 1939, after a normal pregnancy. On November 17, it was noted that he was of good colour but thin, and that his hands and feet were bent upwards and rather stiff. The father said that the infant had the facial appearance of old age since birth. The grand-parents and parents showed none of the characteristics of arachnodactyly and no evidence of this disorder could be found in the two elder brothers. The infant was breast fed for five months and then given condensed milk and subsequently some rice, a little pork, beef and eggs.

Examination. The infant recognized both parents. His mental ability was fair. He followed simple orders from his parents. His face appeared prematurely aged and the forehead wrinkled (fig. 1). The head was asymmetrical. There was a prominent boss on the posterior part of the right frontal region with a corresponding prominence on the opposite occipital region conforming with the description of a plagiocephalic skull. There were also smaller bosses on the posterior part of the left frontal region and in both temporal

regions. The anterior fontanelle had closed, leaving a depression which measured 2 cm. anteroposteriorly and 1 cm. from side to side. Both ears were

FIG. 1.—Photograph of patient. Note the wrinkles on his forehead, deeply-set eyeballs, facial appearance of maturity, funnel-shaped chest and Harrison's sulcus.

FIG. 2.—Photograph of patient. Note the characteristic slender skeletal development, the long narrow thorax, the long hands and feet, the long fingers and toes.

large and soft and deficient in cartilage. The bulbus oculi were deeply set. The hard palate was deeply arched and the two upper and lower incisor teeth were present.

He weighed 12 lb. 14 oz. and had the slender skeletal development characteristic of arachnodactyly (fig. 2). There was generalized absence of subcutaneous

FIG. 3.—Hand of patient marked B in the photograph contrasted with the hand of a normally formed Chinese infant, aged eight months, marked A.

FIG. 4.—Foot of patient marked B in the photograph contrasted with the foot of a normally formed Chinese infant, aged 8 months, marked A.

fat. The thorax was long and narrow. The chest was funnel-shaped and there was a Harrison's sulcus. He could neither sit up nor crawl. The musculature was poorly developed and there was a high degree of asthenia. The hands and

fingers and the feet and toes were long and slender (fig. 3 and 4). Pes planus and a spur-like projection of the calcaneus (fig. 5) were present. The left thumb showed a fixed flexion deformity at the metacarpo-phalangeal joint (fig. 6).

FIG. 5.—Foot of the patient showing spur-like projection of the calcaneus and pes planus.

There was unusual laxity of the ligaments at the knee and ankle-joints, enabling the infant to maintain the grotesque attitude of his legs seen in fig. 7.

There was congenital heart disease, manifested by diffuse praecordial pulsation, systolic murmurs over the pulmonary and tricuspid areas, and an accentuated pulmonary second sound.

The superficial and deep reflexes were present. The pupils were equal and

FIG. 6.—Left hand of patient showing the thumb contracted and flexed into the palm of the hand at the metacarpo-phalangeal joint.

small and reacted readily to light. The infant could recognize his parents and follow a bright light. An examination of the eyes was carried out under general anaesthesia by Dr. R. D. Williamson who reported: ' There is marked megalo-

cornea with very high myopia. It is impossible to make out the details of the fundus and it cannot be established if the lenses are dislocated or not. The

FIG. 7.—Note the grotesque position of the legs adopted by the patient.

intra-ocular pressure in each eye is 15 mm. Hg (normal 15 to 25 mm. Hg).'

There was bilateral otitis media and the right testis was undescended.

The following measurements give a comparison between the patient and a normal Chinese infant aged eight months :—

	PATIENT AGED 7½ MONTHS	NORMAL CHINESE INFANT AGED 8 MONTHS
	All measurements in inches	
Length	28·4	24·0
Circumference of head	17·2	16·8
Arm	4·6	4·4
Forearm	4·4	3·6
Hand (from mid-point of wrist to tip of middle finger)	4·2	2·8
Thigh	5·4	6·0
Leg	5·0	5·4
Foot (from heel to tip of big toe)	5·0	4·2

The above measurements make clear the following points:—

1. The patient is 4·4 inches longer than the normal Chinese infant of eight months and his length is equal to the length of a normal American infant of 10½ months (Mead's chart compiled by Arthur I. Blau).

2. The length of the hand is only 0·2 inches less than the length of the forearm while the difference is 0·6 inches in the normal Chinese infant.

3. The length of the patient's foot is equal to the length of his leg whereas in the normal Chinese infant there is a difference of 1·2 inches.

X-ray examination by Dr. J. W. Winchester, Radiologist to the General Hospital, revealed a double scoliosis of the spinal column (fig. 8) and no abnormality in the appearance of the epiphysis was detected.

The Kahn test on the blood was negative. The patient had an attack of

bacillary dysentery of the Flexner type, and was discharged from hospital on July 22, 1940.

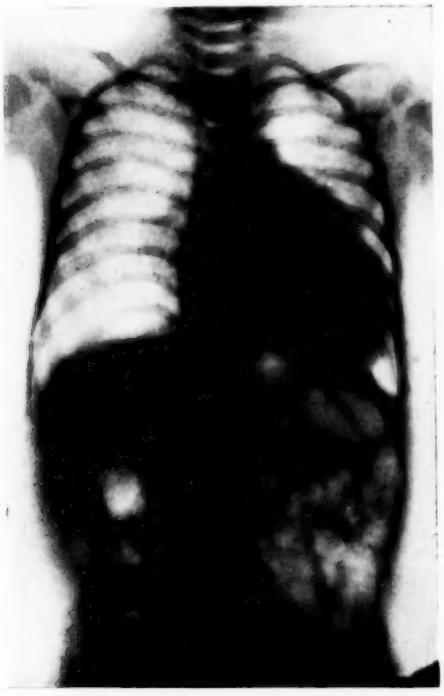

FIG. 8.—Skiagram of spine of patient showing double scoliosis.

Comment

This is the first case of arachnodactyly in a Chinese infant recorded in Malaya. The infant was first taken to hospital when he was five months old, at which time Little's disease was suspected. As it is said that the characteristic features of arachnodactyly are not usually noticed until the infant is two or three years old, we were fortunate in finding them, associated with ocular defects, in this patient at the age of seven-and-a-half months. Ocular defects are present in only half the cases, and are not essential for diagnosis. The familial and hereditary nature of the condition was not exemplified in this case, but isolated examples of the condition are known to occur. Some indication of the early presence of arachnodactyly can be gathered from the infant's welfare card where on the twelfth day it was stated that the infant was thin, and at three-and-a-half months that the infant was ' big but thin.' (The welfare nurse probably meant ' long and thin.') This infant's skull was asymmetrical and was of the plagiocephalic type. The patient also showed the classical combination of congenital morbus cordis with arachnodactyly (Piper and Irvine-Jones, 1926).

Summary

(1) A case of arachnodactyly is reported in a Chinese Cantonese infant of seven-and-a-half months.

(2) This is the first case of its kind reported in Malaya.

(3) Nearly all the characteristic features of the disease were recognized in this patient at an unusually early age.

(4) Particular features of the case are the appearance of premature senescence; the abnormal length of the infant as a whole and of the hands and feet in particular; and the presence of congenital morbus cordis.

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EXTENSIVE CONGENITAL MALFORMATION OF THE SKIN

BY

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The following case is of some interest on account of the unusual extent of the deformity produced, and the difficulty of assigning to it any adequate explanation. The accompanying photographs illustrate well the condition seen (fig. 1 and 2).

FIG. 1.

History. The child, baby G., was the seventh child of an apparently healthy mother aged forty-two. The previous confinements had been normal, and the children healthy, except for one case of spina bifida.

The pregnancy in this case had lasted, as far as could be determined, for about thirty-four weeks, and there had been no untoward symptoms. The

membranes ruptured spontaneously on December 1, 1938, but pains did not begin until nearly seven days later, on December 7, at 9 p.m. After about twelve hours, pains became irregular, so the attendant midwife gave a hot douche, following which contractions increased, and the child was born a few minutes later, at 9.30 a.m. on December 8. The third stage was prolonged and attempts at expression having failed, the doctor who had been summoned sent the patient into hospital with the baby. On admission the mother was in fair condition, though slightly shocked, and there had been no bleeding ; morphine was given, and after a few hours rest the placenta was removed manually.

Physical examination. The child appeared to be of thirty-four to thirty-six

FIG. 2.

weeks' development; length 17½ inches; weight 3 lb. 6 oz.; skull 11 inches in circumference. The child was quite lively, and in good condition, but had a slight talipes equinus deformity in the right foot. The most striking feature was a large linear marking of the skin extending in a hook shape from above and in front of the left ear, behind the pinna, down the neck and left side of the body to the thigh, as far as the knee, with a secondary mark extending on to the outer side of the left arm. In places this linear mark broadened to about an inch, and its depth varied from a slight superficial erythema to actual ulceration of the skin. In places there was apparent granulation tissue and some well-defined fibrous-tissue formation, which appeared to have contracted on the neck; the whole condition resembled very closely a healing second and third degree burn.

Progress. The mother made excellent progress and produced adequate

supplies of milk, on which the child gained weight satisfactorily. After a fortnight, as the mother had many household cares, she was allowed to go home, and attended twice daily for expression of milk. The Wassermann reaction of the mother's blood was negative. Performance of the test on the child was, rather unfortunately, postponed, as the child was discharged from hospital quite healthy after a month, but returned ten days later with broncho-pneumonia, and died.

The progress of the malformation exactly followed that of a burn with rapid healing under a paraffin dressing. Moderately severe scar contracture occurred, especially in the neck, and produced before death a mild degree of torticollis.

Post-mortem examination on the child showed broncho-pneumonia but no other lesion, and the healing scar presented no abnormality, consisting of simple fibrous tissue, with a moderate round cell infiltration, and no sign of any of the granulomas, or of unusual blood-vessel formation or pigmentation.

Careful investigation was made into the history of the whole pregnancy and confinement. The mother strongly and repeatedly denied any interference whatever at any time, and apart from the douche given by the nurse shortly before birth, there appears to have been no possibility of trauma.

Discussion

The cause of congenital malformations such as talipes, intrauterine amputations of fingers and ears, and ' dimpling ' of the skin has been widely discussed. Browne (1936) has produced considerable evidence in support of intra-uterine pressure as a factor in most of the common malformations, and has suggested (personal communication) that lack of liquor amnii with resulting pressure and abrasion may be responsible for a malformation such as that described here. This case, however, presents several unusual features. The deformity was extensive, and indeed I can find no record of any other case with an injury of the skin of any comparable extent. The involvement of the hollow of the neck and the duplication on both arm and body of the same appearance are difficult to explain by a pressure theory. If the latter were the cause, it would have been expected that only the more prominent and therefore the most exposed parts would show the greatest involvement, whereas the neck hollow appears to have suffered the most damage and also the earliest, as healing was most marked here. The extent of the formation of fibrous tissue at birth suggested that the healing had been going on for a greater period than seven days (during which time the membranes had been ruptured), though it is recognized that this is a doubtful criterion, as healing in utero is probably greatly in excess of the normal. The maternal Wassermann reaction was negative, and though the factor of recent pregnancy might modify the value of this, I consider that a syphilitic history can be excluded when this negative is considered in conjunction with the obstetric history, the appearances of the child, and the absence of histological signs of syphilis in the scar at post-mortem.

It appears possible that such an injury might be produced by an attempt to procure abortion by the intra-uterine use of an instrument early in pregnancy: before flexion of the head for example, a linear injury might result, later becoming curved as development proceeded.

Such a theory, however, presents many objections. It seems unlikely that use of an instrument at a later date, after the formation of the amniotic sac, could injure the foetus without also rupturing the membranes and producing

abortion. It is possible that such an attempt may have been made ten days or so before birth, but some injury to the mother with such an extensive lesion in the child would have been expected.

Against the possibility of injury must be set the fact that the mother appeared to be a decent honest person, who was most distressed by the appearance of the child, and persistent in her denials of any interference either by herself or others.

Summary

1. A case is described of a widespread congenital skin malformation.
2. Various possible causes are discussed.
3. It is shown that injury by an instrument, or pressure due to deficient liquor, as a cause for the deformity, is not fully consistent with all the facts.

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SUPPURATIVE PERIARTHRITIS IN AN INFANT DUE TO THE SUIPESTIFER BACILLUS

BY

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Salmonella infections in infancy and early childhood show a marked tendency to invade the blood-stream and produce foci of suppuration in various organs and tissues. Certain strains appear to become localized in particular sites; thus b. enteritidis (Gaertner's bacillus) and the closely related b. dublin, frequently infect the meninges causing suppurative meningitis. B. suipestifer (the hog cholera bacillus), on the other hand, tends rather to produce lesions in bones and joints. The following case of suipestifer infection illustrates involvement of the periarticular tissues of the right shoulder joint.

Case report

The subject, a male infant aged seven months, was admitted to hospital on November 19, 1937. For the previous week he had been irritable, screaming when the right arm was moved. He did not use the arm above the elbow though able to move the fingers. Apart from a 'cold' during the previous two months he had always been healthy and the bowels had been regular. He had been breast fed. On examination the child was pale and had an upper respiratory infection. The right shoulder was fuller than the left and there was tenderness on attempting movement of the right arm. The upper part of the humerus also was sensitive to pressure. On x-ray examination the day after admission an arthritis of the right shoulder joint was diagnosed. Signs of broncho-pneumonia rapidly developed followed by nuchal rigidity and increased irritability. Lumbar puncture was performed on November 22, when the cerebro-spinal fluid was under slightly increased pressure. Microscopic examination, however, showed no noteworthy increase in cells and no organisms and cultures remained sterile. Death occurred on November 23, 1937.

Post-mortem findings. At autopsy exploration of the right shoulder joint revealed a collection of thick yellow pus round the joint chiefly on the anterior and inferior aspects. This was not confined to any of the related bursae. The joint capsule was intact and the joint itself was not inflamed and was free from effusion. No pus was found when the right femur was split lengthwise. The lungs showed pus in the bronchioles with patchy broncho-pneumonia of suppurative type at both bases. Nothing else of note was present in the thorax. There was no gross morbid change in the liver and kidneys, and the stomach and intestines were normal. The spleen was of septic type. Abundant pus was present in both middle ears. There was no meningitis and the brain substance was normal.

Bacteriology. Films of the periarticular pus showed scanty Gram-negative coliform bacilli. Cultures made in broth yielded a pure growth of a Gram-negative actively motile bacillus, and on MacConkey plates the colonies were all of non-lactose-fermenting type. Several were subcultured and produced acid and gas in glucose, mannite and maltose. Lactose, saccharose and dulcite were not fermented and no indole was formed. These reactions suggested that the strain belonged to the Salmonella group and confirmation was obtained on testing with a polyvalent Salmonella serum (Oxford standards) which agglutinated it to titre. Pus from both ears also yielded a non-lactose-fermenting growth similar in all respects to that obtained from the periarticular pus. Cultures were next tested against a paratyphosus B antiserum of high titre, but no agglutination occurred even in a dilution of 1/100. Other Salmonella antisera gave a negative result with the exception of paratyphosus C antiserum (Oxford standards) which agglutinated cultures practically to titre, thus suggesting that the organism might be a strain of b. suipestifer which belongs to the paratyphosus C group. The unknown Yorkhill culture was then further investigated along with Lister Institute strains of the two common suipestifer types—American and European (Kunzendorf). The series of biological tests to which the three cultures were subjected was the same as that employed by Guthrie and Montgomery (1939). All three strains gave similar fermentation reactions, rapidly producing acid and gas in sorbite, rhamnose and xylose and failing even after a week to ferment arabinose, trehalose and dextrin. All were negative in Bitter's arabinose and rhamnose and in Stern's glycerin-fuchsin bouillon. A heavy precipitate occurred in d-tartrate medium. Gelatin was not liquified. The Voges-Proskauer reaction was negative and litmus milk was rendered slightly alkaline. The strains varied in their behaviour towards lead acetate, the Yorkhill and the standard Kunzendorf culture both blackening this substance within twenty-four hours while the American strain completely failed to do so even after a week. Behaviour towards lead acetate is considered of importance in distinguishing between the American and Kunzendorf types, since the latter forms H_2S while the former does not. According to Bergey (1939) b. suipestifer typically ferments dulcite and dextrin with the production of acid and gas. The culture in the present case as well as the two Lister Institute strains failed to do so even after incubation for one week. It is well recognized, however, that in the Salmonella group there is a marked tendency to cultural variations, the serological characters being more stable (Kauffmann, 1934, 1935–36; Havens, 1935). Serological tests were then undertaken to complete the identification of the Yorkhill organism. That it possessed the O (somatic) antigens VI and VII of the paratyphosus C group was proved by the fact that an O antiserum prepared from a standard Lister Institute strain of b. paratyphosus C agglutinated it practically to titre. These O antigens are shared in common by b. paratyphosus C and by both the American and European strains of b. suipestifer. The H (flagellar) antigenic formula of the last two differs in that the American strain is biphasic possessing the specific flagellar fraction c in addition to the non-specific fractions 1, 3, 4, 5, while the Kunzendorf variant is monophasic, having an identical non-specific antigenic formula, but lacking the specific c fraction. Antisera prepared in rabbits to the standard American and European suipestifer strains and to the unknown Yorkhill organism, agglutinated reciprocally all three cultures to approximately the same high titre, showing that all had common flagellar antigens. The next step in identification was the absorption of all the non-specific agglutinins from a suipestifer antiserum. The unknown Yorkhill organism, if monophasic, would then fail to agglutinate. Accordingly a heavy Kunzendorf growth was used to exhaust an antiserum to the American suipestifer strain, when the titre for the Yorkhill as well as for the stock Kunzendorf culture dropped from

1/25,000 to less than 1/400. On the other hand, the American strain was still agglutinated in high dilution by virtue of its unabsorbed specific flagellar fraction c. The Yorkhill organism was thus found to be monophasic, its serological as well as its main biological reactions corresponding with those of b. suipestifer var. Kunzendorf. The monophasic nature of the Yorkhill culture was confirmed by repeated testing, using on each occasion a number of isolated colonies from several plates. The toxicity of the strain was determined by rabbit inoculation. An animal weighing 2·3 kgm. survived the intravenous inoculation of 1/100 of a fresh agar culture suspended in saline, but 1/10 of a culture killed a 3 kgm. animal within twenty-four hours. A heavy pure growth of the infecting organism was recovered from the heart blood, spleen and bile, and the intestinal flora at different levels consisted almost entirely of suipestifer colonies.

Discussion

Recognition of the pathogenicity for human beings of the suipestifer group of organisms dates largely from the last war when such infections were rife in eastern Europe, producing mainly paratyphoid-like disease. Originally b. suipestifer was considered pathogenic only for pigs in which it was thought to cause swine fever. It is now known, however, that here it plays the part merely of a secondary invader, the actual etiological agent being a filterable virus.

White (1926) classified suipestifer strains into four main types (a) American, (b) Eastern (Hirschfeld), (c) Western European, (d) Glässer-Voldagsen. Topley and Wilson (1936) regard the Glässer and Voldagsen strains as distinct although both are included in the 'Ferkeltyphus' bacilli of the German literature which produce typhoid-like disease in pigs, but so far as is known do not infect man. Within recent years human cases of suipestifer infection have been recorded in many parts of the world, occurring both in epidemic and sporadic form. Smith (1934) ranks the European type of b. suipestifer fifth in order of frequency among the Salmonella strains causing sporadic infections in this country. This is the most widespread suipestifer strain according to Boycott and McNee (1936), who state that only seven proved human infections with the American type are on record and that no certain infection with the Eastern (b. paratyphosus C) strain has occurred in Britain. In epidemics the type of disease produced is acute gastro-enteritis, diverse articles of food having been incriminated as the source of infection. Large outbreaks are reported by Schnitter (1927), Stewart and Litterer (1927); the occurrence of smaller epidemics is mentioned by Boller (1930) and Harvey (1937). In sporadic cases the organism may cause a gastro-intestinal type of disease simulating an enteric infection, or it may invade the blood-stream producing septicaemia with metastatic abscesses.

It appears from a survey of the literature that children are more susceptible than adults to suipestifer infection. White (1929), in reviewing the subject, states 'A disproportionately large number of the cases (of European suipestifer infection), especially those of abscess formation, occurred in infants and children; and most of those among adults are referable to the period of the War or the immediately succeeding years.' Nabarro et al. (1929) also regard the European strain as particularly apt to attack young children and to occur as frequently in localized disease as in general febrile infection and gastro-enteritis. Harvey (1937), reviewing a series of seventy-one suipestifer infections, mostly collected

from the literature, found the majority of sporadic cases occurring in the first decade. Similarly of the twenty-eight cases reported by Ravitch and Washington (1937) almost all were in children. There is considerable diversity in the lesions produced by b. suipestifer. The typhoid-like clinical course is exemplified by the cases of Kuttner and Zepp (1932). Urinary excretion was observed by Rau (1932) in an infant with septicaemia. Gouley and Israel (1934) saw what appeared to be a true endocarditis arising during the course of a suipestifer septicaemia. B. suipestifer in addition to pneumococcus was cultured by Steuer (1937) from an empyema in a child aged three years. A pure growth of the former organism was recovered from an abscess which developed later in the thigh muscles. Clifton and Werner (1938) isolated a suipestifer strain from a sub-dural abscess. In the case of Ravitch and Washington this organism was grown from the cerebro-spinal fluid, but was thought by the authors to be derived actually from blood present in the specimen as the blood culture was positive. Whilst these examples serve to illustrate the protean nature of suipestifer infection, one particular lesion appears to predominate, especially in infants, i.e. septic arthritis. In Harvey's series skeletal disease was present in fifteen cases (approximately 20 per cent.) of which seven were infants in the first year of life. It is difficult to explain this localization, since trauma to the bones and joints would be less likely to occur in infancy than in later life. In fact, no history of injury is given in most of the recorded cases, the joint swelling having appeared insidiously. A number of cases which closely resemble that here recorded are reported in the literature. Thus Langwill (1921) records septicaemia in an infant with arthritis of the left shoulder joint, pus from which yielded an organism of the Salmonella group agglutinated by paratyphosus C antiserum.

Nabarro et al. saw infection of both shoulder joints in a female infant aged eight months, and isolated from the pus a typical American suipestifer strain. A joint lesion due to the European type in a child is also mentioned in their paper. The case reported by Bosch (1929) was an eleven-months-old infant with pus in the right knee-joint. Suipestifer infection in twins is described by Van Creveld and Ruys (1933). The first was admitted to hospital with a respiratory infection, and appeared at autopsy to have an ordinary broncho-pneumonia with fibrinous pleurisy. Pneumonia was also diagnosed in the second twin who developed otitis media while in hospital. Later, in the course of the disease, the right knee suddenly swelled and a suipestifer strain was isolated from the blood-stained pus obtained by paracentesis, and also from the faeces. Tur and Gartoch (1934) observed a young infant whose mother died of a typhoid-like disease eighteen days post-partum. The child developed successively swelling of the right hand, right knee-joint, right shoulder and left ankle, in addition to a spreading broncho-pneumonia. A suipestifer strain was recovered from pus in the shoulder joint and from the faeces. Death occurred at the age of thirty-three days. A suppurative lesion affecting the right shoulder joint is recorded by Teveli (1935) in a child aged fifteen months who had pneumonia in addition. The sputum, however, was negative for the Salmonella organism. The case of Gajzágó and Göttche (1935) bears a close similarity to the one here reported, since the lesion recorded by these authors, which also affected the shoulder in a young infant, was probably periarticular and not actually within the joint cavity. On x-ray examination the diaphysis of the humerus in their patient showed rarefaction

thus suggesting the presence of an associated osteomyelitis. The rare condition of spinal osteomyelitis in the course of a suipestifer infection was seen in a child by Harvey (1937).

It is of interest that in the present case as well as in those of Teveli, Tur and Gartoch, Van Creveld and Ruys, pneumonia was associated with the articular lesion. It is not clear if the pulmonary lesion in the instances mentioned was actually of suipestifer origin, since no bacteriological data are given with regard to the lungs, except in Teveli's patient in whom the sputum was negative for b. suipestifer. In the present case cultures were not made from the lungs since the pneumonia appeared to be of ordinary suppurative type. The frequency of pulmonary complications in association with other lesions due to b. suipestifer is, however, emphasized by various writers.

Harvey found pulmonary or pleural involvement in one-third of the cases in his series. Cole and Nalls (1938) give a similar figure, and Haynes and Meiks (1933) consider the pulmonary type of suipestifer infection second only in frequency to the intestinal. A pure growth of b. suipestifer was actually isolated by Bullowa (1928) from an adult case which was clinically one of typical lobar pneumonia, and Harvey states that in six instances the diagnosis of a suipestifer lung infection was confirmed bacteriologically.

There appear to be grounds, therefore, for believing that pneumonia, when it occurs in the course of a suipestifer infection, is actually due to this organism.

Whilst it must be assumed that in suipestifer, as in other Salmonella infections, the portal of entry is the digestive tract, it is of interest that frequently no intestinal lesion is found at autopsy. This was true in the present case and in those of other investigators. Thus Cole and Nalls state that there is generally no morbid change in the gastro-intestinal tract and Boycott and McNee are of the opinion that intestinal ulcers are rare in suipestifer infections. Further, this organism is rarely isolated from the faeces. For example, in the series reported by Kuttner and Zepp it was recovered from the faeces of only one patient in seven, though repeated investigations were carried out in the majority. Other writers confirm the fact that faeces examination is generally negative, though blood cultures are frequently positive. As with other Salmonella strains the organism may enter by way of the pharynx, as suggested by Guerra et al. (1940). These authors instance the case of a child with a Salmonella septicaemia which began as a severe rhinopharyngitis followed by bilateral suppurative otitis media. The fact that the present patient also had a bilateral otitis and a history of a 'cold' before the onset of the joint swelling, lends support to the hypothesis of a rhinopharyngeal portal of entry.

The source of suipestifer, like other sporadic Salmonella infections, is generally quite obscure as in the present instance. There is seldom a history of association with another patient, and only occasionally in the literature is there any history of contact with diseased pigs. Proof that these animals are not necessarily concerned in the spread of such infections is afforded by the experience of Neukirch (1918) who observed cases due to b. paratyphosus C in Turkey where the rearing of pigs is prohibited by the Mohammedan creed. It must be assumed that the suipestifer bacillus is ingested in contaminated food.

The high morbidity rate in children may depend on the fact that as compared with adults they have less resistance to infection and hence may be susceptible to a relatively small inoculum.

Summary

A case is described of suipestifer infection in an infant with the characteristic localization in relation to a joint. The literature on suipestifer infection in children is shortly reviewed.

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